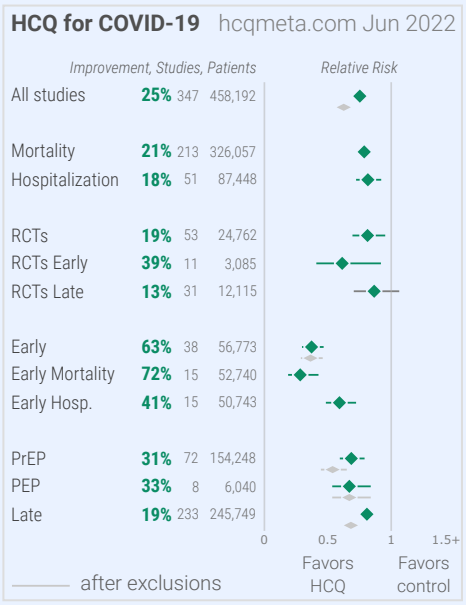
HCQ for COVID-19: real-time meta analysis of 347 studies

Covid Analysis, **June 5, 2022**, Version 214 — added Tu
https://hcqmeta.com/

- Meta analysis using the most serious outcome reported shows 63% [53-70%] improvement for the 38 early treatment studies. Results are similar after exclusion based sensitivity analysis and after restriction to peer-reviewed studies. The 11 RCTs show 39% [8-59%] improvement, and the 15 mortality results shows 72% [57-81%] lower mortality.
- 21 early treatment studies show statistically significant improvements in isolation (15 for the most serious outcome).
- Late treatment is less successful, with only 67% of the 233 studies reporting a positive effect. Very late stage treatment is not effective and may be harmful, especially when using excessive dosages.



- 78% of Randomized Controlled Trials (RCTs) for early, PrEP, or PEP treatment report positive effects, the probability of results as good or better for an ineffective treatment is 0.0053.
- There is evidence of bias towards publishing negative results. 76% of prospective studies report positive effects, compared to 71% of retrospective studies. Studies from North America are 2.6 times more likely to report negative results than studies from the rest of the world combined, p = 0.0000000191.
- Negative meta analyses of HCQ generally choose a subset of trials, focusing on late treatment, especially trials with very late treatment and excessive dosages.
- While many treatments have some level of efficacy, they do not replace vaccines and other measures to avoid infection. Only 5% of HCQ studies show zero events in the treatment arm. Multiple treatments are typically used in combination, which may be significantly more effective.
- No treatment, vaccine, or intervention is 100% available and effective for all variants. All practical, effective, and safe means should be used. Denying the efficacy of treatments increases mortality, morbidity, collateral damage, and endemic risk.
- All data to reproduce this paper and the sources are in the appendix. See ***[Ladapo, Prodromos, Risch, Risch (B)]*** for other meta analyses showing efficacy when HCQ is used early.

Total	347 studies	5,474 authors	458,769 patients
Positive effects	251 studies	3,861 authors	329,123 patients

Early treatment	63% improvement	RR 0.37 [0.30-0.47]

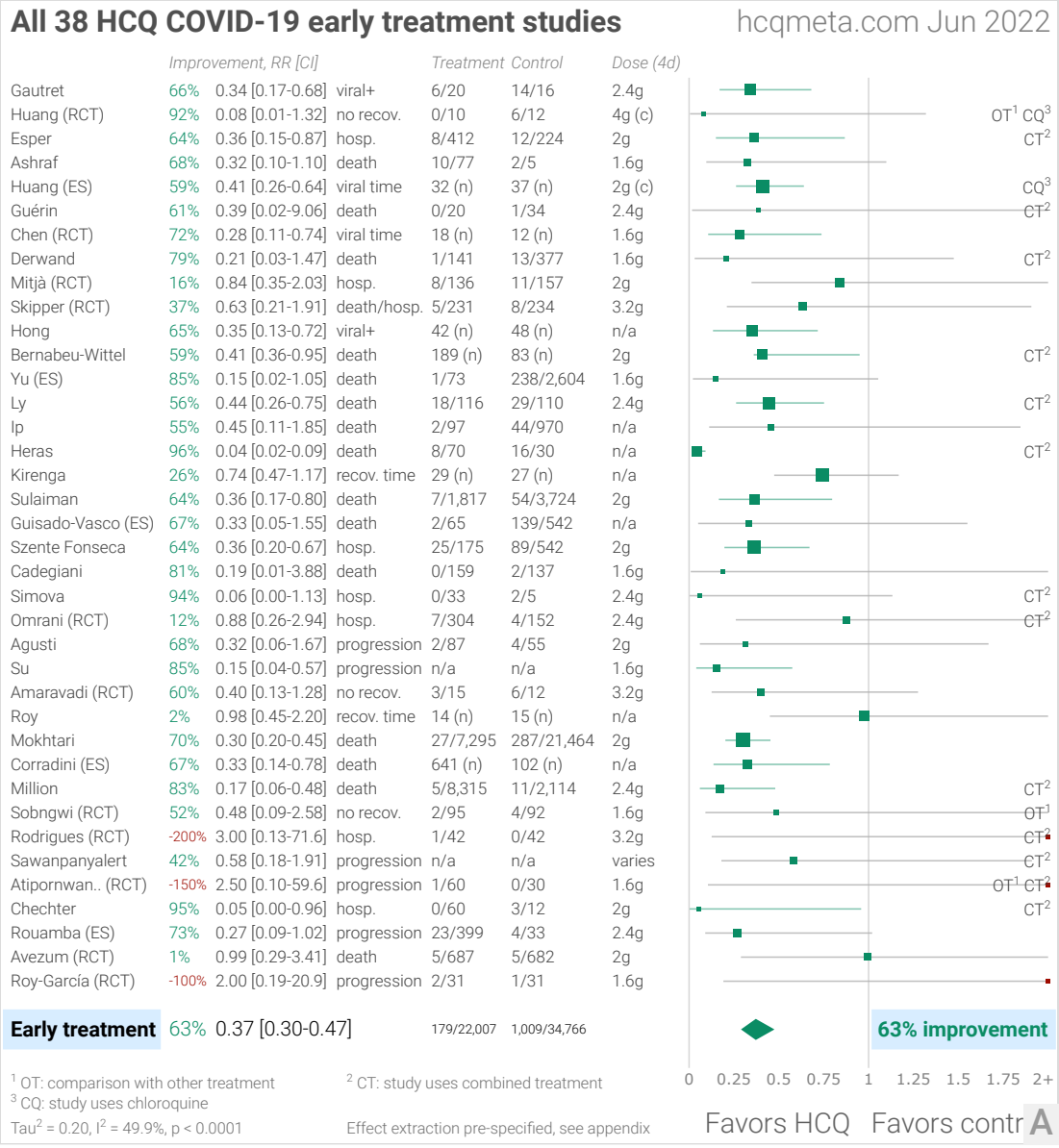
Late treatment	19% improvement	RR 0.81 [0.76-0.86]

HIGHLIGHTS

HCQ reduces risk for COVID-19 with very high confidence for mortality, hospitalization, cases, viral clearance, and in pooled analysis.

We show traditional outcome specific analyses and combined evidence from all studies, incorporating treatment delay, a primary confounding factor in COVID-19 studies.

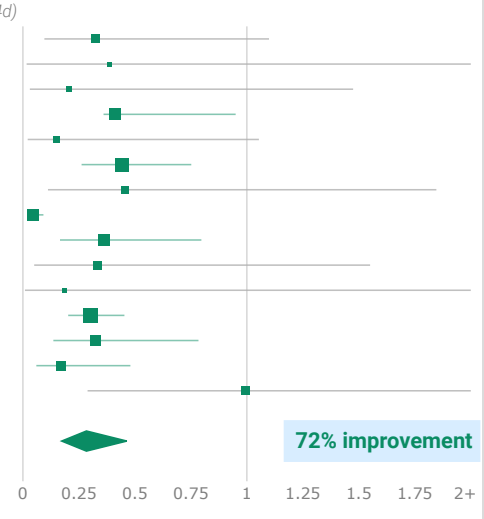
Real-time updates and corrections, transparent analysis with all results in the same format, consistent protocol for 42 treatments.



All 15 HCQ COVID-19 mortality early treatment results

hcqmeta.com Jun 2022

	Improvement, RR [CI]	Treatment	Control	Dose (4d)
Ashraf	68% 0.32 [0.10-1.10]	10/77	2/5	1.6g
Guérin	61% 0.39 [0.02-9.06]	0/20	1/34	2.4g
Derwand	79% 0.21 [0.03-1.47]	1/141	13/377	1.6g
Bernabeu-Wittel	59% 0.41 [0.36-0.95]	189 (n)	83 (n)	2g
Yu (ES)	85% 0.15 [0.02-1.05]	1/73	238/2,604	1.6g
Ly	56% 0.44 [0.26-0.75]	18/116	29/110	2.4g
Ip	55% 0.45 [0.11-1.85]	2/97	44/970	n/a
Heras	96% 0.04 [0.02-0.09]	8/70	16/30	n/a
Sulaiman	64% 0.36 [0.17-0.80]	7/1,817	54/3,724	2g
Guisado-Vasco (ES)	67% 0.33 [0.05-1.55]	2/65	139/542	n/a
Cadegiani	81% 0.19 [0.01-3.88]	0/159	2/137	1.6g
Mokhtari	70% 0.30 [0.20-0.45]	27/7,295	287/21,464	2g
Corradini (ES)	67% 0.33 [0.14-0.78]	641 (n)	102 (n)	n/a
Million	83% 0.17 [0.06-0.48]	5/8,315	11/2,114	2.4g
Avezum (RCT)	1% 0.99 [0.29-3.41]	5/687	5/682	2g
Early treatment	72% 0.28 [0.17-0.46]	86/19,762	841/32,978	



$Tau^2 = 0.41$, $I^2 = 68.0\%$, $p < 0.0001$

B

All 15 HCQ COVID-19 hospitalization early treatment results

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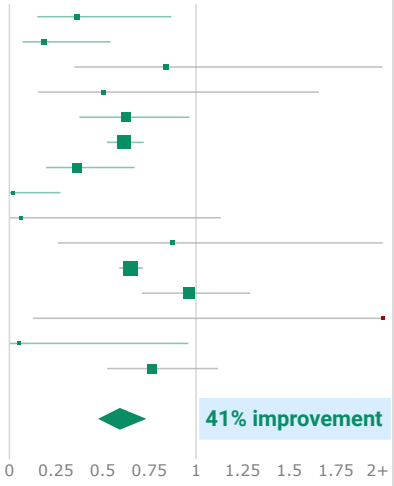
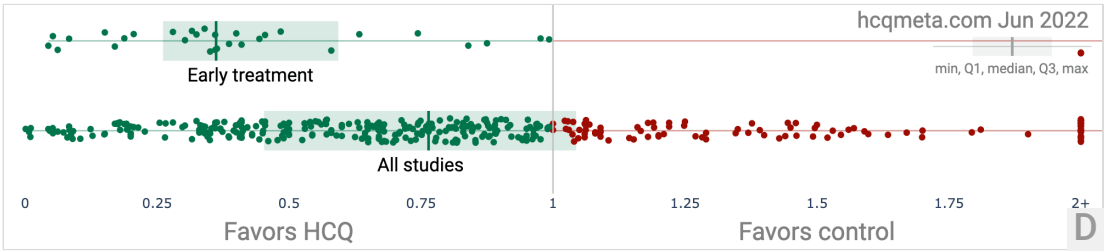
	Improvement, RR [CI]		Treatment	Control	Dose (4d)
Esper	64% 0.36 [0.15-0.87]	hosp.	8/412	12/224	2g
Derwand	82% 0.18 [0.07-0.54]	hosp.	4/141	58/377	1.6g
Mitjà (RCT)	16% 0.84 [0.35-2.03]	hosp.	8/136	11/157	2g
Skipper (RCT)	49% 0.51 [0.15-1.66]	hosp.	4/231	8/234	3.2g
Ip	37% 0.63 [0.37-0.96]	hosp.	21/97	305/970	n/a
Sulaiman	39% 0.61 [0.52-0.72]	hosp.	171/1,817	617/3,724	2g
Szente Fonseca	64% 0.36 [0.20-0.67]	hosp.	25/175	89/542	2g
Cadegiani	98% 0.02 [0.00-0.27]	hosp.	0/159	27/137	1.6g
Simova	94% 0.06 [0.00-1.13]	hosp.	0/33	2/5	2.4g
Omrani (RCT)	12% 0.88 [0.26-2.94]	hosp.	7/304	4/152	2.4g
Mokhtari	35% 0.65 [0.59-0.71]	hosp.	523/7,295	2,382/21,464	2g
Million	4% 0.96 [0.71-1.29]	hosp.	214/8,315	64/2,114	2.4g
Rodrigues (RCT)	-200% 3.00 [0.13-71.6]	hosp.	1/42	0/42	3.2g
Chechter	95% 0.05 [0.00-0.96]	hosp.	0/60	3/12	2g
Avezum (RCT)	23% 0.77 [0.52-1.12]	hosp.	44/689	57/683	2g
Early treatment	41% 0.59 [0.48-0.72]		1,030/19,906	3,639/30,837	



$Tau^2 = 0.05$, $I^2 = 63.5\%$, $p < 0.0001$

C



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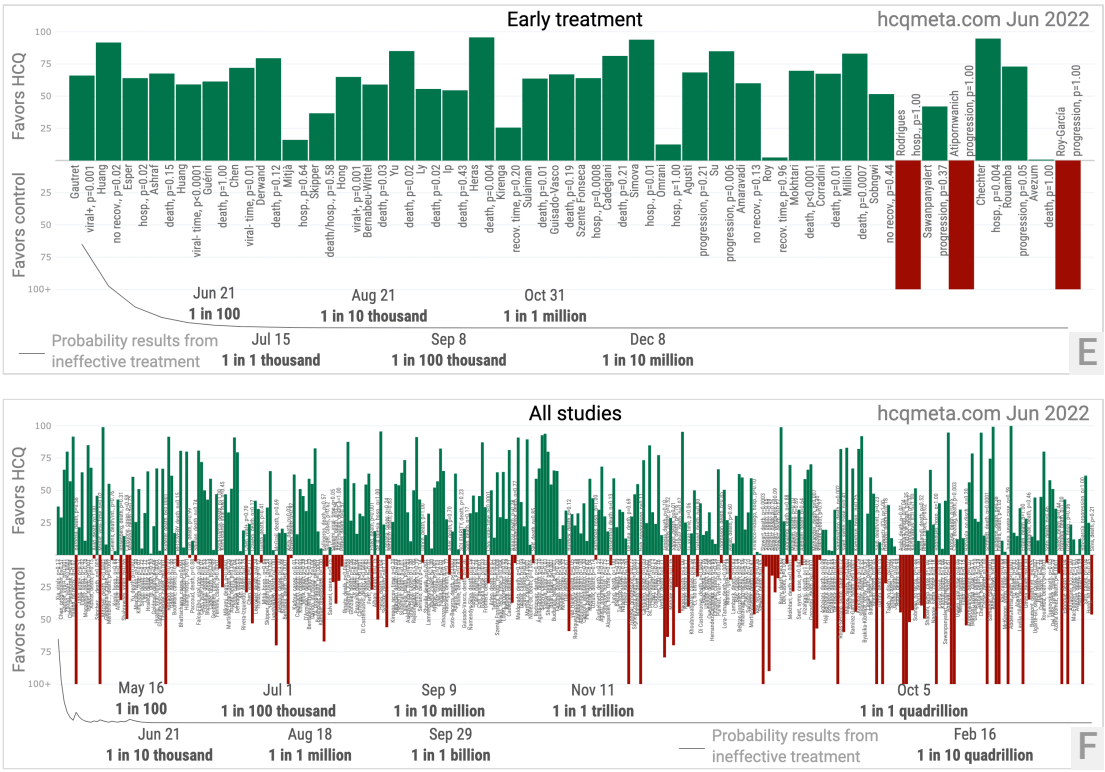

Figure 1. *A. Random effects meta-analysis of all early treatment studies. This plot shows pooled effects, analysis for individual outcomes is below, and more details on pooled effects can be found in the heterogeneity section. Effect extraction is pre-specified, using the most serious outcome reported. Simplified dosages are shown for comparison, these are the total dose in the first four days. Chloroquine is indicated with (c). For details of effect extraction and full dosage information see the appendix.* ***B and C.*** *Random effects meta-analysis of all early treatment mortality and hospitalization results.* ***D.*** *Scatter plot of the effects reported in early treatment studies and in all studies. Early treatment is more effective.* ***E and F.*** *Chronological history of all reported effects, with the probability that the observed or greater frequency of positive results were generated by an ineffective treatment.*

Introduction

We analyze all significant studies concerning the use of HCQ (or CQ) for COVID-19. Search methods, inclusion criteria, effect extraction criteria (more serious outcomes have priority), all individual study data, PRISMA answers, and statistical methods are detailed in Appendix 1. We present random-effects meta-analysis results for all studies, for studies within each treatment stage, for mortality results only, after exclusion of studies with critical bias, and for Randomized Controlled Trials (RCTs) only. Typical meta analyses involve subjective selection criteria and bias evaluation, requiring an understanding of the criteria and the accuracy of the evaluations. However, the volume of studies presents an opportunity for an additional simple and transparent analysis aimed at detecting efficacy.

If treatment was not effective, the observed effects would be randomly distributed (or more likely to be negative if treatment is harmful). We can compute the probability that the observed percentage of positive results (or higher) could occur due to chance with an ineffective treatment (the probability of >= *k* heads in *n* coin tosses, or the one-sided sign test / binomial test). Analysis of publication bias is important and adjustments may be needed if there is a bias toward publishing positive results. For HCQ, we find evidence of a bias toward publishing negative results.

Figure 2 shows stages of possible treatment for COVID-19. **Pre-Exposure Prophylaxis (PrEP)** refers to regularly taking medication before being infected, in order to prevent or minimize infection. In **Post-Exposure Prophylaxis (PEP)**, medication is taken after exposure but before symptoms appear. **Early Treatment** refers to treatment immediately or soon after symptoms appear, while **Late Treatment** refers to more delayed treatment.

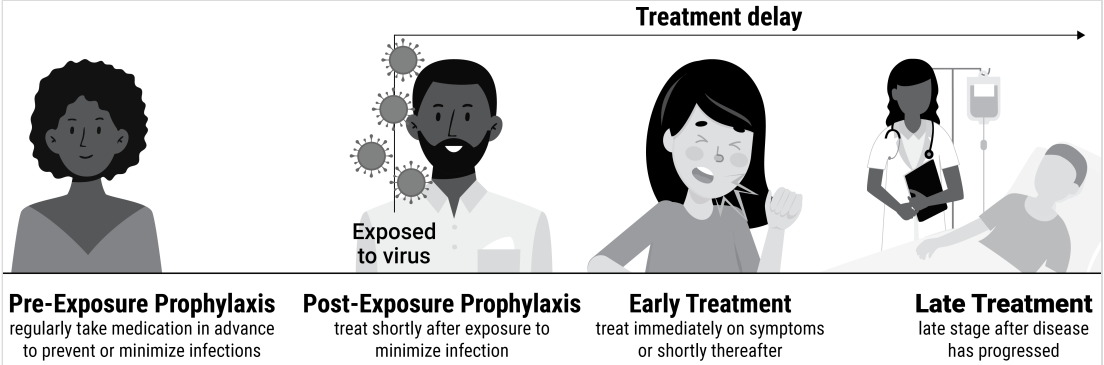

Figure 2. *Treatment stages.*

Preclinical and Phase I Research

5 *In Silico* studies support the efficacy of hydroxychloroquine ***[Baildya, Hussein, Noureddine, Tarek, Yadav]***.

13 *In Vitro* studies support the efficacy of hydroxychloroquine ***[Andreani, Clementi, Dang, Delandre, Faísca, Hoffmann, Liu, Ou, Purwati, Sheaff, Wang, Wang (B), Yao]***.

An *In Vivo* animal study supports the efficacy of hydroxychloroquine ***[Maisonnasse]***.

3 studies investigate novel formulations of hydroxychloroquine that may be more effective for COVID-19 ***[Faísca, Klimke, Zelenko]***.

[Kavanagh] present a phase I clinical study investigating a novel formulation of hydroxychloroquine that may be more effective for COVID-19.

Preclinical research is an important part of the development of treatments, however results may be very different in clinical trials. Preclinical results are not used in this paper.

Results

Figure 3 shows a visual overview of the results. Figure 4, Figure 5, and Table 1 show results by treatment stage, and Figure 6 shows a forest plot for a random effects meta-analysis of all studies. Figure 7 and Figure 8 show forest plots restricted to mortality and hospitalization results only.

Early treatment. 92% of early treatment studies report a positive effect, with an estimated reduction of 63% in the effect measured (death, hospitalization, etc.) from the random effects meta-analysis, RR 0.37 [0.30-0.47].

Late treatment. Late treatment studies are mixed, with 67% showing positive effects, and an estimated reduction of 19% in the random effects meta-analysis. Negative studies mostly fall into the following categories: they show evidence of significant unadjusted confounding, including confounding by indication; usage is extremely late; or they use an excessively high dosage.

Pre-Exposure Prophylaxis. 78% of PrEP studies show positive effects, with an estimated reduction of 31% in the random effects meta-analysis. Negative studies are all studies of systemic autoimmune disease patients which either do not adjust for the different baseline risk of these patients at all, or do not adjust for the highly variable risk within these patients.

Post-Exposure Prophylaxis. 88% of PEP studies report positive effects, with an estimated reduction of 33% in the random effects meta-analysis.

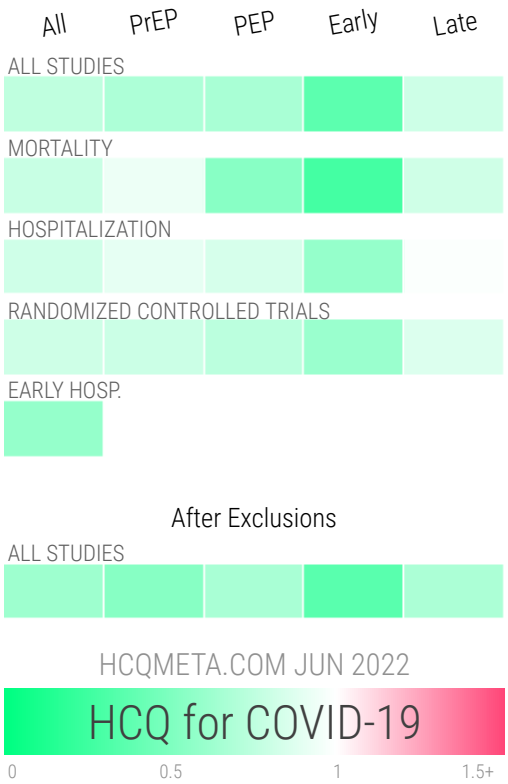

Figure 3. *Overview of results.*

Treatment time	Number of studies reporting positive results	Total number of studies	Percentage of studies reporting positive results	Probability of an equal or greater percentage of positive results from an ineffective treatment	Random effects meta-analysis results
Early treatment	35	38	**92.1%**	1 in 30 million	**63%** improvement RR 0.37 [0.30-0.47] p < 0.0001
Late treatment	157	234	67.1%	1 in 11 million	19% improvement RR 0.81 [0.76-0.86] p < 0.0001
Pre-Exposure Prophylaxis	57	73	78.1%	1 in 1 million	31% improvement RR 0.69 [0.59-0.79] p < 0.0001
Post-Exposure Prophylaxis	7	8	87.5%	1 in 28	33% improvement RR 0.67 [0.53-0.84] p = 0.0005
All studies	251	347	72.3%	1 in 49 quadrillion	25% improvement RR 0.75 [0.71-0.79] p < 0.0001

Table 1. *Results by treatment stage. 6 studies report results for a subset with early treatment, these are not included in the overall results.*

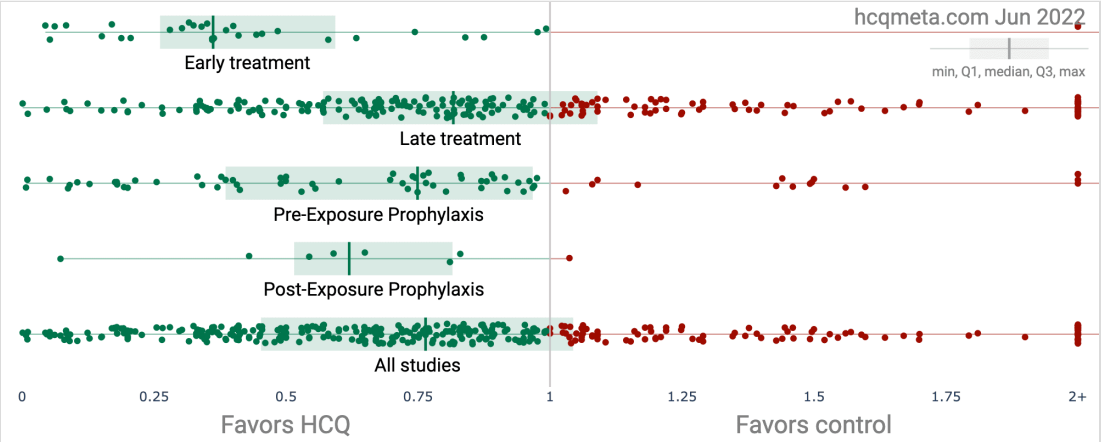

Figure 4. *Results by treatment stage.*

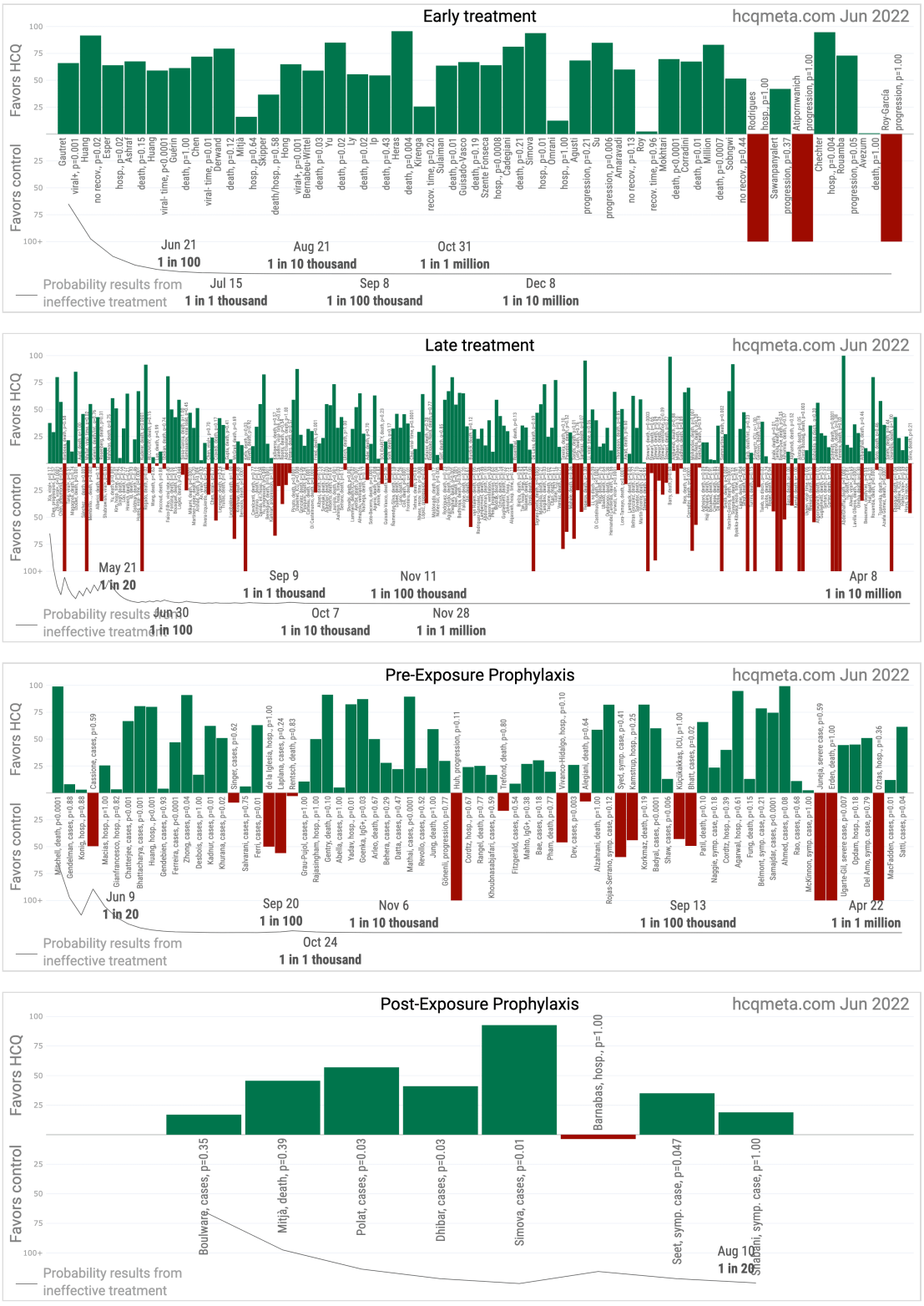

Figure 5. *Chronological history of results by treatment stage, with the probability that the observed or greater frequency of positive results were generated by an ineffective treatment.*

All hydroxychloroquine COVID-19 studies

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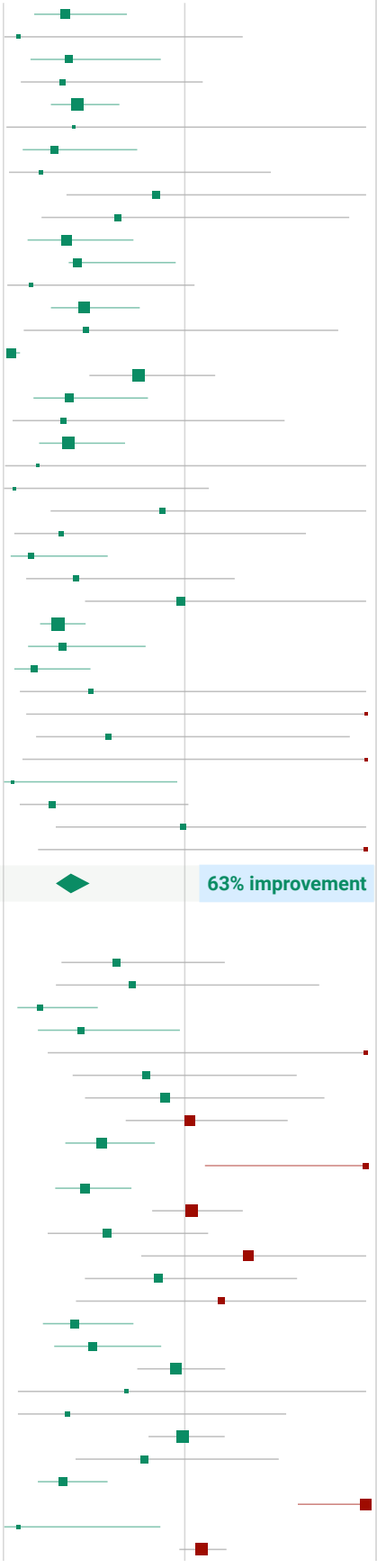
	Improvement	RR [CI]		Treatment	Control
Gautret	66%	0.34 [0.17-0.68]	viral+	6/20	14/16
Huang (RCT)	92%	0.08 [0.01-1.32]	no recov.	0/10	6/12
Esper	64%	0.36 [0.15-0.87]	hosp.	8/412	12/224
Ashraf	68%	0.32 [0.10-1.10]	death	10/77	2/5
Huang (ES)	59%	0.41 [0.26-0.64]	viral time	32 (n)	37 (n)
Guérin	61%	0.39 [0.02-9.06]	death	0/20	1/34
Chen (RCT)	72%	0.28 [0.11-0.74]	viral time	18 (n)	12 (n)
Derwand	79%	0.21 [0.03-1.47]	death	1/141	13/377
Mitjà (RCT)	16%	0.84 [0.35-2.03]	hosp.	8/136	11/157
Skipper (RCT)	37%	0.63 [0.21-1.91]	death/hosp.	5/231	8/234
Hong	65%	0.35 [0.13-0.72]	viral+	42 (n)	48 (n)
Bernabeu-Wittel	59%	0.41 [0.36-0.95]	death	189 (n)	83 (n)
Yu (ES)	85%	0.15 [0.02-1.05]	death	1/73	238/2,604
Ly	56%	0.44 [0.26-0.75]	death	18/116	29/110
Ip	55%	0.45 [0.11-1.85]	death	2/97	44/970
Heras	96%	0.04 [0.02-0.09]	death	8/70	16/30
Kirenga	26%	0.74 [0.47-1.17]	recov. time	29 (n)	27 (n)
Sulaiman	64%	0.36 [0.17-0.80]	death	7/1,817	54/3,724
Guisado-Vasco (ES)	67%	0.33 [0.05-1.55]	death	2/65	139/542
Szente Fonseca	64%	0.36 [0.20-0.67]	hosp.	25/175	89/542
Cadegiani	81%	0.19 [0.01-3.88]	death	0/159	2/137
Simova	94%	0.06 [0.00-1.13]	hosp.	0/33	2/5
Omrani (RCT)	12%	0.88 [0.26-2.94]	hosp.	7/304	4/152
Agusti	68%	0.32 [0.06-1.67]	progression	2/87	4/55
Su	85%	0.15 [0.04-0.57]	progression	n/a	n/a
Amaravadi (RCT)	60%	0.40 [0.13-1.28]	no recov.	3/15	6/12
Roy	2%	0.98 [0.45-2.20]	recov. time	14 (n)	15 (n)
Mokhtari	70%	0.30 [0.20-0.45]	death	27/7,295	287/21,464
Corradini (ES)	67%	0.33 [0.14-0.78]	death	641 (n)	102 (n)
Million	83%	0.17 [0.06-0.48]	death	5/8,315	11/2,114
Sobngwi (RCT)	52%	0.48 [0.09-2.58]	no recov.	2/95	4/92
Rodrigues (RCT)	-200%	3.00 [0.13-71.6]	hosp.	1/42	0/42
Sawanpanyalert	42%	0.58 [0.18-1.91]	progression	n/a	n/a
Atipornwan.. (RCT)	-150%	2.50 [0.10-59.6]	progression	1/60	0/30
Chechter	95%	0.05 [0.00-0.96]	hosp.	0/60	3/12
Rouamba (ES)	73%	0.27 [0.09-1.02]	progression	23/399	4/33
Avezum (RCT)	1%	0.99 [0.29-3.41]	death	5/687	5/682
Roy-García (RCT)	-100%	2.00 [0.19-20.9]	progression	2/31	1/31
Early treatment	63%	0.37 [0.30-0.47]		179/22,007	1,009/34,766

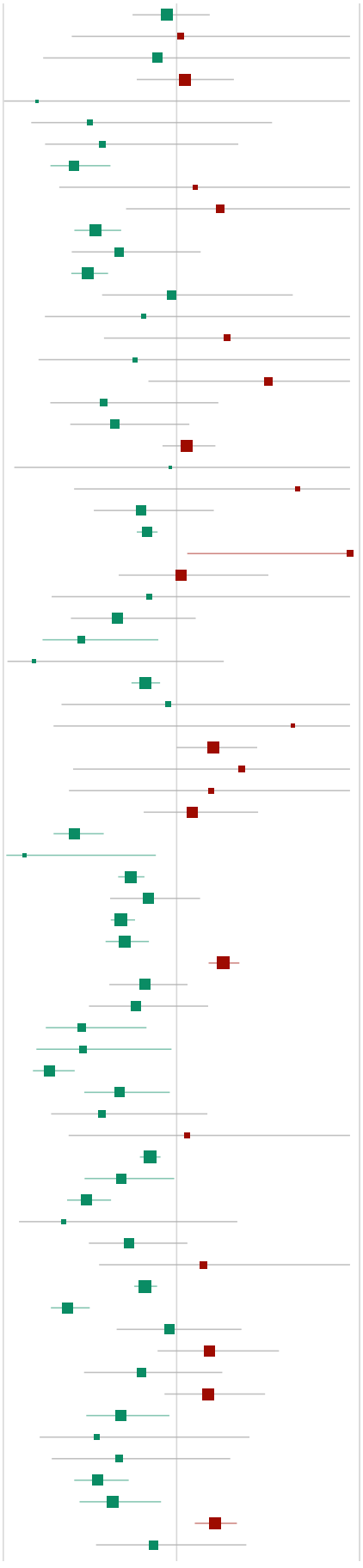
63% improvement

$Tau^2 = 0.20$, $I^2 = 49.9\%$, $p < 0.0001$

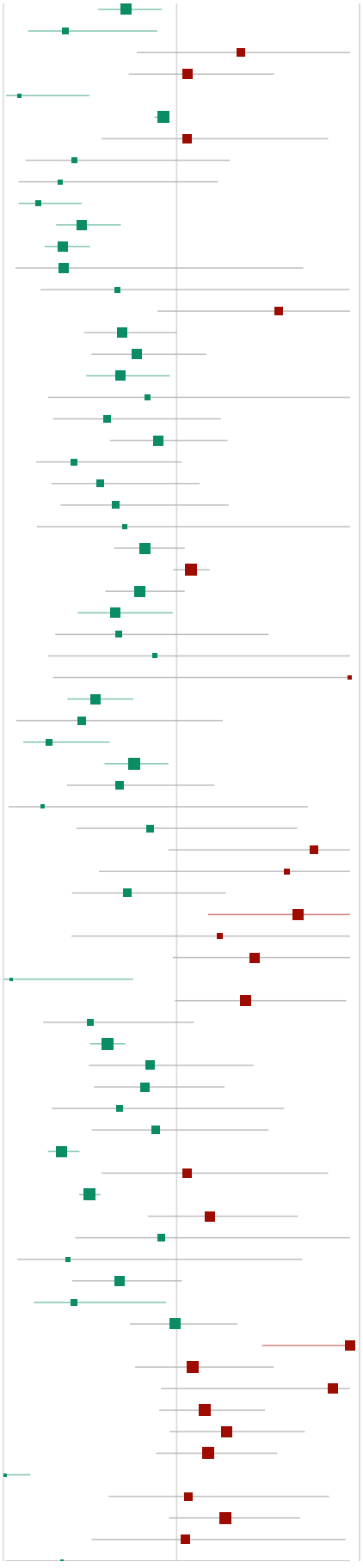
	Improvement	RR [CI]		Treatment	Control
Xia	38%	0.62 [0.32-1.22]	viral+	5/10	12/15
Chen (RCT)	29%	0.71 [0.29-1.74]	progression	5/15	7/15
Zhong	80%	0.20 [0.08-0.52]	viral+	5/115	17/82
Chen (RCT)	57%	0.43 [0.19-0.97]	pneumonia	6/31	14/31
Barbosa	-147%	2.47 [0.24-25.0]	death	2/17	1/21
Tang (RCT)	21%	0.79 [0.38-1.62]	viral+	11/75	14/75
Magagnoli	11%	0.89 [0.45-1.77]	death	39/148	18/163
Auld	-3%	1.03 [0.67-1.57]	death	33/114	29/103
Sánchez-Álvarez	46%	0.54 [0.34-0.84]	death	322 (n)	53 (n)
Mallat	-203%	3.03 [1.11-7.69]	viral time	23 (n)	11 (n)
Membrillo de No..	55%	0.45 [0.29-0.71]	death	27/123	21/43
Geleris	-4%	1.04 [0.82-1.32]	death/int.	262/811	84/565
Alberici	43%	0.57 [0.24-1.13]	death	17/72	9/22
Rosenberg	-35%	1.35 [0.76-2.40]	death	189/735	28/221
Shabrawishi	15%	0.85 [0.45-1.62]	viral+	12/45	15/48
Mahévas	-20%	1.20 [0.40-3.30]	death	9/84	8/89
Yu	60%	0.40 [0.22-0.72]	death	9/48	238/502
Kim	51%	0.49 [0.28-0.87]	hosp. time	22 (n)	40 (n)
Singh	5%	0.95 [0.74-1.22]	death	104/910	109/910
Luo	32%	0.68 [0.08-5.88]	death	19 (n)	264 (n)
Hraiech (ICU)	65%	0.35 [0.08-1.56]	death	2/17	5/15
Ip	1%	0.99 [0.80-1.22]	death	432/1,914	115/598
Goldman	22%	0.78 [0.40-1.52]	death	10/109	34/288
Huang	67%	0.33 [0.19-0.57]	viral time	197 (n)	176 (n)
Kuderer	-134%	2.34 [1.62-3.21]	death	45/181	121/928
Rogado	92%	0.08 [0.00-0.87]	death	1/8	7/9
RECOVERY (RCT)	-9%	1.09 [0.97-1.23]	death	421/1,561	790/3,155

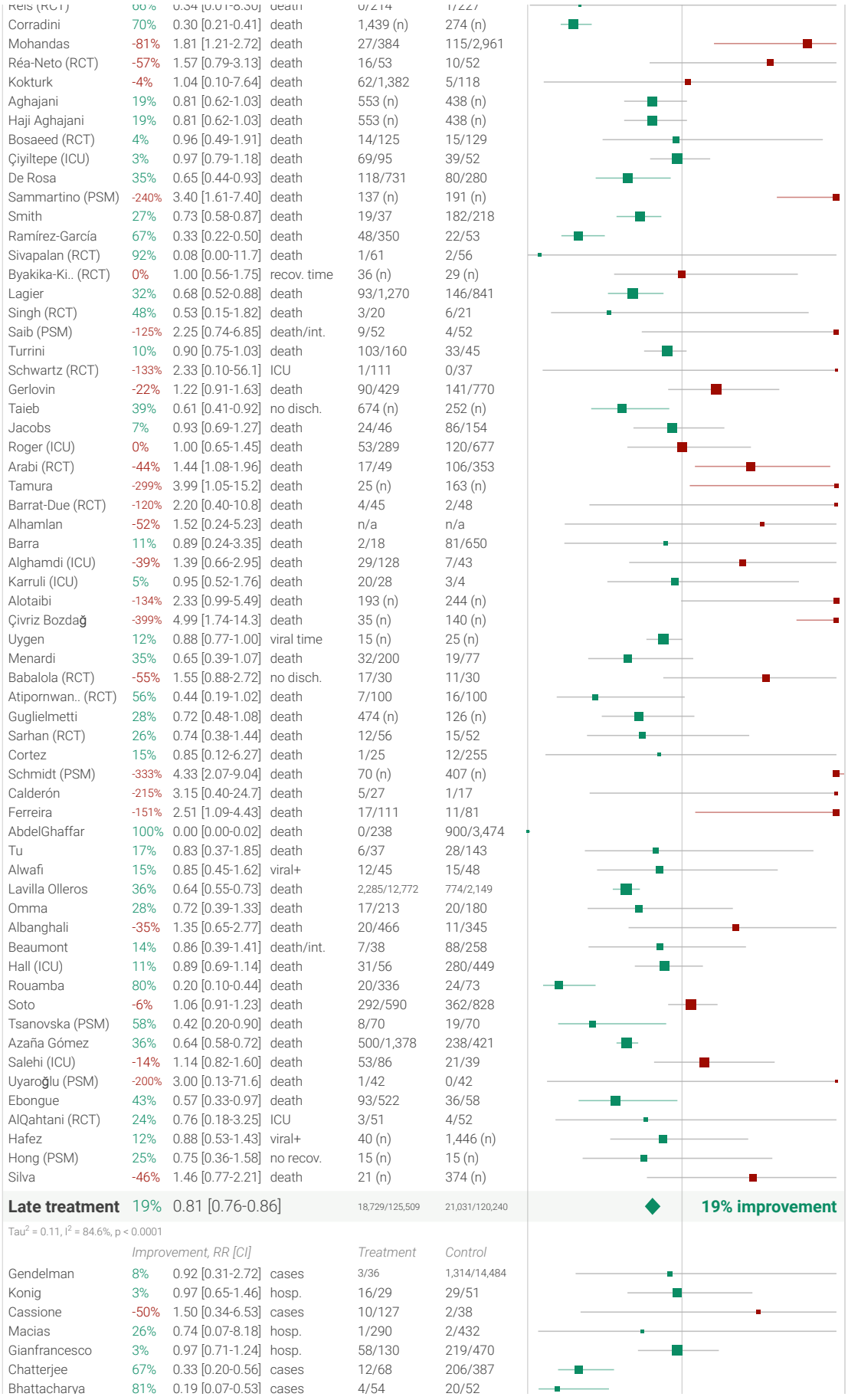


Wang	6%	0.94 [0.75-1.19]	death	1,866 (n)	5,726 (n)
Luo	-2%	1.02 [0.39-2.65]	death	11/35	4/13
Paccoud	11%	0.89 [0.23-3.47]	death	21/38	26/46
Sbidian	-5%	1.05 [0.77-1.33]	death	111/623	830/3,792
Faíco-Filho	81%	0.19 [0.00-8.66]	viral rate	34 (n)	32 (n)
Fontana	50%	0.50 [0.16-1.55]	death	4/12	2/3
Bousquet	43%	0.57 [0.24-1.36]	death	5/27	23/81
Lagier	59%	0.41 [0.27-0.62]	death	35/3,119	58/618
Sosa-García (ICU)	-11%	1.11 [0.32-3.78]	death	7/38	3/18
Komissarov	-25%	1.25 [0.71-2.21]	viral load	26 (n)	10 (n)
Mikami	47%	0.53 [0.41-0.68]	death	575/2,077	231/743
Martinez-Lopez	33%	0.67 [0.39-1.14]	death	47/148	9/19
Arshad	51%	0.49 [0.39-0.60]	death	162/1,202	108/409
An	3%	0.97 [0.57-1.67]	viral+	31 (n)	195 (n)
Rivera-Izquierdo	19%	0.81 [0.24-2.76]	death	215 (n)	23 (n)
Chen	-29%	1.29 [0.58-2.86]	viral+	16/28	4/9
Chen (RCT)	24%	0.76 [0.20-2.84]	viral+	4/21	3/12
Cravedi	-53%	1.53 [0.84-2.80]	death	36/101	10/43
Lecronier (ICU)	42%	0.58 [0.27-1.24]	death	9/38	9/22
Trullàs	36%	0.64 [0.39-1.07]	death	20/66	16/34
Gupta	-6%	1.06 [0.92-1.22]	death	631/1,761	153/454
Lyngbakken (RCT)	4%	0.96 [0.06-14.6]	death	1/27	1/26
McGrail	-70%	1.70 [0.41-7.07]	death	4/33	3/42
Krishnan	20%	0.80 [0.52-1.21]	death	86/144	6/8
Bernaola	17%	0.83 [0.77-0.89]	death	236/1,498	28/147
Kelly	-143%	2.43 [1.06-5.56]	death	23/82	6/52
Rivera	-2%	1.02 [0.67-1.53]	death	44/179	59/327
Cavalcanti (RCT)	16%	0.84 [0.28-2.53]	death	8/331	5/173
D'Arminio Monfo..	34%	0.66 [0.39-1.11]	death	53/197	47/92
Davido	55%	0.45 [0.23-0.89]	int./hosp.	12/80	13/40
Yu	83%	0.17 [0.02-1.27]	progression	1/231	32/1,291
Berenguer	18%	0.82 [0.74-0.90]	death	681/2,618	438/1,377
Kamran	5%	0.95 [0.34-2.69]	progression	11/349	5/151
Kalligeros	-67%	1.67 [0.29-9.36]	death	36 (n)	72 (n)
Saleemi	-21%	1.21 [1.00-1.46]	viral time	65 (n)	20 (n)
Roomi	-38%	1.38 [0.40-2.76]	death	13/144	6/32
Abd-Elsalam (RCT)	-20%	1.20 [0.38-3.80]	death	6/97	5/97
Peters	-9%	1.09 [0.81-1.47]	death	419/1,596	53/353
Pinato	59%	0.41 [0.29-0.58]	death	30/182	181/446
Dubernet	88%	0.12 [0.02-0.88]	ICU	1/17	9/19
Gonzalez	27%	0.73 [0.66-0.81]	death	1,246/8,476	341/1,168
Pasquini (ICU)	16%	0.84 [0.62-1.14]	death	23/33	15/18
Catteau	32%	0.68 [0.62-0.76]	death	804/4,542	957/3,533
Di Castelnuovo	30%	0.70 [0.59-0.84]	death	386/2,634	90/817
Fried	-27%	1.27 [1.18-1.36]	death	1,048/4,232	1,466/7,489
Albani	18%	0.82 [0.61-1.06]	death	60/211	172/605
Synolaki	24%	0.76 [0.49-1.18]	death	21/98	60/214
Alamdari	55%	0.45 [0.25-0.83]	death	54/427	9/32
Heberto	54%	0.46 [0.19-0.97]	death	139 (n)	115 (n)
Lauriola	74%	0.27 [0.17-0.41]	death	102/297	35/63
Ashinyo	33%	0.67 [0.47-0.96]	hosp. time	61 (n)	61 (n)
Serrano	43%	0.57 [0.28-1.18]	death	6/14	6/8
Ulrich (RCT)	-6%	1.06 [0.38-2.98]	death	7/67	6/61
Shoaibi	15%	0.85 [0.79-0.91]	death	686/5,047	3,923/24,404
Lammers	32%	0.68 [0.47-0.99]	death/ICU	30/189	101/498
Ayerbe	52%	0.48 [0.37-0.62]	death	237/1,857	49/162
Almazrou	65%	0.35 [0.09-1.35]	ventilation	3/95	6/66
Nachega	28%	0.72 [0.49-1.06]	death	69/630	28/96
Ader (RCT)	-15%	1.15 [0.55-2.27]	death	11/150	13/149
Soto-Becerra	18%	0.82 [0.76-0.89]	death	346/692	1,606/2,630
Aparisi	63%	0.37 [0.27-0.50]	death	122/605	27/49
Annie	4%	0.96 [0.65-1.37]	death	48/367	50/367
SOLIDARITY (RCT)	-19%	1.19 [0.89-1.59]	death	104/947	84/906
Guisado-Vasco	20%	0.80 [0.47-1.26]	death	127/558	14/49
Solh	-18%	1.18 [0.93-1.51]	death	131/265	134/378
Ñamendys-S.. (ICU)	32%	0.68 [0.48-0.96]	death	24/54	42/64
Dubee (RCT)	46%	0.54 [0.21-1.42]	death	6/124	11/123
Lano	33%	0.67 [0.28-1.31]	death	56 (n)	66 (n)
Coll	46%	0.54 [0.41-0.72]	death	55/307	108/328
Frontera (PSM)	37%	0.63 [0.44-0.91]	death	121/1,006	424/2,467
Choi	-22%	1.22 [1.10-1.35]	viral time	701 (n)	701 (n)
Tehrani	13%	0.87 [0.54-1.40]	death	16/65	54/190



Niwas	29%	0.71 [0.55-0.91]	recov. time	12 (n)	17 (n)
López	64%	0.36 [0.14-0.89]	progression	5/36	14/36
Salazar	-37%	1.37 [0.77-2.42]	death	12/92	80/811
Rodriguez-Nava	-6%	1.06 [0.72-1.56]	death	22/65	79/248
Maldonado	91%	0.09 [0.02-0.50]	death	1/11	1/1
Núñez-Gil	8%	0.92 [0.87-0.94]	death	200/686	100/268
Self (RCT)	-6%	1.06 [0.57-1.87]	death	25/241	25/236
Rodriguez	59%	0.41 [0.13-1.31]	death	8/39	2/4
Águila-Gordo	67%	0.33 [0.09-1.24]	death	151/346	47/70
Sheshah	80%	0.20 [0.09-0.45]	death	267 (n)	33 (n)
Boari	55%	0.45 [0.30-0.68]	death	41/202	25/56
Budhiraja	65%	0.35 [0.24-0.50]	death	69/834	34/142
Falcone (PSM)	65%	0.35 [0.07-1.73]	death	40/238	30/77
Qin	34%	0.66 [0.22-2.00]	death	3/43	75/706
Burdick	-59%	1.59 [0.89-2.83]	death	142 (n)	148 (n)
van Halem	32%	0.68 [0.47-1.00]	death	34/164	47/155
Rodriguez-Gonzalez	23%	0.77 [0.51-1.17]	death	251/1,148	17/60
Lambermont	32%	0.68 [0.48-0.96]	death	97/225	14/22
Abdulrahman (PSM)	17%	0.83 [0.26-2.69]	death	5/223	6/223
Capsoni	40%	0.60 [0.29-1.25]	ventilation	12/40	6/12
Peng	11%	0.89 [0.62-1.29]	progression	29/453	256/3,567
Modrák	59%	0.41 [0.19-1.03]	death	108 (n)	105 (n)
Ozturk	44%	0.56 [0.28-1.13]	death	165/1,127	6/23
Guglielmetti	35%	0.65 [0.33-1.30]	death	181 (n)	37 (n)
Johnston (RCT)	30%	0.70 [0.19-2.54]	hosp.	5/148	4/83
Alqassieh	18%	0.82 [0.64-1.05]	hosp. time	63 (n)	68 (n)
Rosenthal	-8%	1.08 [0.98-1.19]	death	n/a	n/a
Bielza	22%	0.78 [0.59-1.05]	death	33/91	249/539
Tan	35%	0.65 [0.43-0.98]	hosp. time	8 (n)	277 (n)
Naseem	33%	0.67 [0.30-1.53]	death	77 (n)	1,137 (n)
Orioli	13%	0.87 [0.26-2.94]	death	8/55	3/18
De Luna	-105%	2.05 [0.29-14.6]	death	15/132	1/18
Signes-Costa	47%	0.53 [0.37-0.75]	death	4,854 (n)	993 (n)
Matangila	55%	0.45 [0.07-1.27]	death	25/147	8/13
Cangiano	73%	0.27 [0.12-0.61]	death	5/33	37/65
Taccone (ICU)	25%	0.75 [0.58-0.95]	death	449/1,308	183/439
Chari	33%	0.67 [0.37-1.22]	death	8/29	195/473
Güner	77%	0.23 [0.03-1.76]	ICU	604 (n)	100 (n)
Vernaz (PSM)	15%	0.85 [0.42-1.70]	death	12/93	16/105
Texeira	-79%	1.79 [0.95-3.38]	death	17/65	14/96
Psevdos	-63%	1.63 [0.55-4.84]	death	17/52	3/15
Mahale	29%	0.71 [0.40-1.28]	death	25/102	11/32
Sands	-70%	1.70 [1.18-2.42]	death	101/973	56/696
Lotfy	-25%	1.25 [0.39-3.96]	death	6/99	5/103
Sarfaraz	-45%	1.45 [0.98-2.15]	death	40/94	27/92
Yegerov	95%	0.05 [0.00-0.75]	death	0/23	20/1,049
Li	-40%	1.40 [0.99-1.98]	viral time	18 (n)	19 (n)
Li	50%	0.50 [0.23-1.10]	no disch.	14 (n)	14 (n)
Di Castelnuovo	40%	0.60 [0.50-0.70]	death	3,270 (n)	1,000 (n)
Roig	16%	0.84 [0.49-1.44]	death	33/67	7/12
Ubaldo (ICU)	18%	0.82 [0.52-1.28]	death	17/25	5/6
Ouedraogo	33%	0.67 [0.28-1.62]	death	397 (n)	59 (n)
Hernandez-C.. (RCT)	12%	0.88 [0.51-1.53]	death	106 (n)	108 (n)
Purwati (RCT)	66%	0.34 [0.26-0.44]	viral+	38/121	111/119
Thompson (RCT)	-6%	1.06 [0.57-1.87]	death	25/241	25/236
Lora-Tamayo	50%	0.50 [0.44-0.56]	death	7,192 (n)	1,361 (n)
Awad	-19%	1.19 [0.84-1.70]	death	56/188	37/148
Lamback	9%	0.91 [0.41-2.00]	death	11/101	11/92
Beltran Gon.. (RCT)	63%	0.37 [0.08-1.73]	death	2/33	6/37
Salvador	33%	0.67 [0.40-1.03]	death	28/121	58/124
Martin-Vice.. (ICU)	59%	0.41 [0.18-0.94]	death	37/91	1/1
Stewart	1%	0.99 [0.73-1.35]	death	66/578	188/1,243
Stewart	-130%	2.30 [1.49-3.54]	death	32/108	33/256
Stewart	-9%	1.09 [0.76-1.56]	death	212/1,157	203/1,101
Stewart	-90%	1.90 [0.91-4.10]	death	46/208	47/1,334
Stewart	-16%	1.16 [0.90-1.51]	death	428/1,711	123/688
Stewart	-29%	1.29 [0.96-1.74]	ventilation	48/305	95/1,302
Stewart	-18%	1.18 [0.88-1.58]	death	90/429	141/737
Barry	99%	0.01 [0.00-0.16]	death	0/6	91/599
Alghamdi	-7%	1.07 [0.61-1.88]	death	44/568	15/207
Mulhem	-28%	1.28 [0.96-1.71]	death	435/2,496	81/723
Gadhiya	-5%	1.05 [0.51-1.97]	death	22/55	33/216
Reis (RCT)	66%	0.34 [0.01-8.30]	death	0/214	1/227





Reis (RCT)	66%	0.34 [0.01-8.30]	death	0/214	1/227
Corradini	70%	0.30 [0.21-0.41]	death	1,439 (n)	274 (n)
Mohandas	-81%	1.81 [1.21-2.72]	death	27/384	115/2,961
Réa-Neto (RCT)	-57%	1.57 [0.79-3.13]	death	16/53	10/52
Kokturk	-4%	1.04 [0.10-7.64]	death	62/1,382	5/118
Aghajani	19%	0.81 [0.62-1.03]	death	553 (n)	438 (n)
Haji Aghajani	19%	0.81 [0.62-1.03]	death	553 (n)	438 (n)
Bosaeed (RCT)	4%	0.96 [0.49-1.91]	death	14/125	15/129
Çiyiltepe (ICU)	3%	0.97 [0.79-1.18]	death	69/95	39/52
De Rosa	35%	0.65 [0.44-0.93]	death	118/731	80/280
Sammartino (PSM)	-240%	3.40 [1.61-7.40]	death	137 (n)	191 (n)
Smith	27%	0.73 [0.58-0.87]	death	19/37	182/218
Ramírez-García	67%	0.33 [0.22-0.50]	death	48/350	22/53
Sivapalan (RCT)	92%	0.08 [0.00-11.7]	death	1/61	2/56
Byakika-Ki.. (RCT)	0%	1.00 [0.56-1.75]	recov. time	36 (n)	29 (n)
Lagier	32%	0.68 [0.52-0.88]	death	93/1,270	146/841
Singh (RCT)	48%	0.53 [0.15-1.82]	death	3/20	6/21
Saib (PSM)	-125%	2.25 [0.74-6.85]	death/int.	9/52	4/52
Turrini	10%	0.90 [0.75-1.03]	death	103/160	33/45
Schwartz (RCT)	-133%	2.33 [0.10-56.1]	ICU	1/111	0/37
Gerlovin	-22%	1.22 [0.91-1.63]	death	90/429	141/770
Taieb	39%	0.61 [0.41-0.92]	no disch.	674 (n)	252 (n)
Jacobs	7%	0.93 [0.69-1.27]	death	24/46	86/154
Roger (ICU)	0%	1.00 [0.65-1.45]	death	53/289	120/677
Arabi (RCT)	-44%	1.44 [1.08-1.96]	death	17/49	106/353
Tamura	-299%	3.99 [1.05-15.2]	death	25 (n)	163 (n)
Barrat-Due (RCT)	-120%	2.20 [0.40-10.8]	death	4/45	2/48
Alhamlan	-52%	1.52 [0.24-5.23]	death	n/a	n/a
Barra	11%	0.89 [0.24-3.35]	death	2/18	81/650
Alghamdi (ICU)	-39%	1.39 [0.66-2.95]	death	29/128	7/43
Karruli (ICU)	5%	0.95 [0.52-1.76]	death	20/28	3/4
Alotaibi	-134%	2.33 [0.99-5.49]	death	193 (n)	244 (n)
Çivriz Bozdağ	-399%	4.99 [1.74-14.3]	death	35 (n)	140 (n)
Uygen	12%	0.88 [0.77-1.00]	viral time	15 (n)	25 (n)
Menardi	35%	0.65 [0.39-1.07]	death	32/200	19/77
Babalola (RCT)	-55%	1.55 [0.88-2.72]	no disch.	17/30	11/30
Atipornwan.. (RCT)	56%	0.44 [0.19-1.02]	death	7/100	16/100
Guglielmetti	28%	0.72 [0.48-1.08]	death	474 (n)	126 (n)
Sarhan (RCT)	26%	0.74 [0.38-1.44]	death	12/56	15/52
Cortez	15%	0.85 [0.12-6.27]	death	1/25	12/255
Schmidt (PSM)	-333%	4.33 [2.07-9.04]	death	70 (n)	407 (n)
Calderón	-215%	3.15 [0.40-24.7]	death	5/27	1/17
Ferreira	-151%	2.51 [1.09-4.43]	death	17/111	11/81
AbdelGhaffar	100%	0.00 [0.00-0.02]	death	0/238	900/3,474
Tu	17%	0.83 [0.37-1.85]	death	6/37	28/143
Alwafi	15%	0.85 [0.45-1.62]	viral+	12/45	15/48
Lavilla Olleros	36%	0.64 [0.55-0.73]	death	2,285/12,772	774/2,149
Omma	28%	0.72 [0.39-1.33]	death	17/213	20/180
Albanghali	-35%	1.35 [0.65-2.77]	death	20/466	11/345
Beaumont	14%	0.86 [0.39-1.41]	death/int.	7/38	88/258
Hall (ICU)	11%	0.89 [0.69-1.14]	death	31/56	280/449
Rouamba	80%	0.20 [0.10-0.44]	death	20/336	24/73
Soto	-6%	1.06 [0.91-1.23]	death	292/590	362/828
Tsanovska (PSM)	58%	0.42 [0.20-0.90]	death	8/70	19/70
Azaña Gómez	36%	0.64 [0.58-0.72]	death	500/1,378	238/421
Salehi (ICU)	-14%	1.14 [0.82-1.60]	death	53/86	21/39
Uyaroğlu (PSM)	-200%	3.00 [0.13-71.6]	death	1/42	0/42
Ebongue	43%	0.57 [0.33-0.97]	death	93/522	36/58
AlQahtani (RCT)	24%	0.76 [0.18-3.25]	ICU	3/51	4/52
Hafez	12%	0.88 [0.53-1.43]	viral+	40 (n)	1,446 (n)
Hong (PSM)	25%	0.75 [0.36-1.58]	no recov.	15 (n)	15 (n)
Silva	-46%	1.46 [0.77-2.21]	death	21 (n)	374 (n)
Late treatment	19%	0.81 [0.76-0.86]		18,729/125,509	21,031/120,240
19% improvement					

$Tau^2 = 0.11$, $I^2 = 84.6\%$, $p < 0.0001$

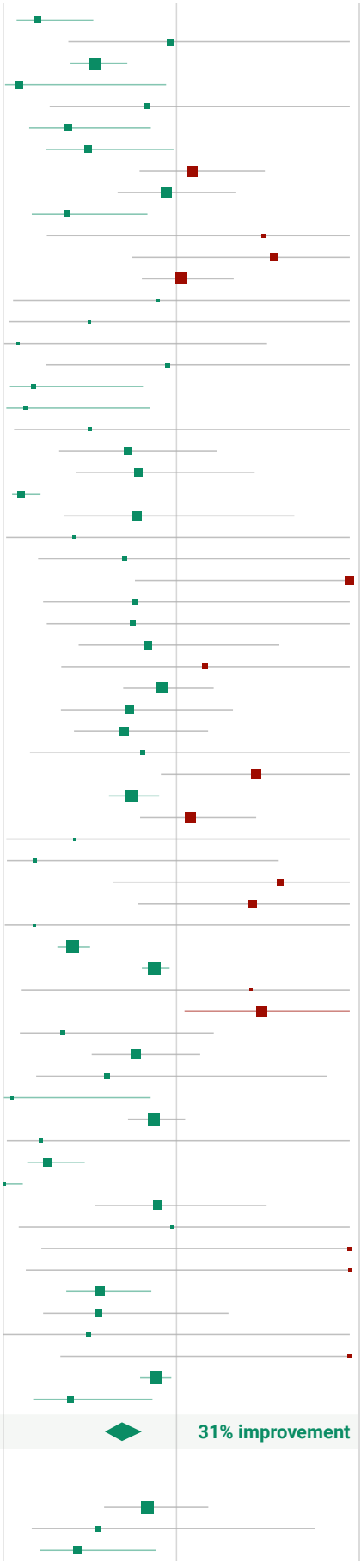
	Improvement, RR [CI]			*Treatment*	*Control*
Gendelman	8%	0.92 [0.31-2.72]	cases	3/36	1,314/14,484
Konig	3%	0.97 [0.65-1.46]	hosp.	16/29	29/51
Cassione	-50%	1.50 [0.34-6.53]	cases	10/127	2/38
Macias	26%	0.74 [0.07-8.18]	hosp.	1/290	2/432
Gianfrancesco	3%	0.97 [0.71-1.24]	hosp.	58/130	219/470
Chatterjee	67%	0.33 [0.20-0.56]	cases	12/68	206/387
Bhattacharya	81%	0.19 [0.07-0.53]	cases	4/54	20/52

Huang	80%	0.20 [0.08-0.52]	hosp.	8 (n)	1,247 (n)
Gendebien	4%	0.96 [0.38-2.46]	cases	12/152	6/73
Ferreira	47%	0.53 [0.39-0.72]	cases	population-based cohort	
Zhong	91%	0.09 [0.01-0.94]	cases	7/16	20/27
Desbois	17%	0.83 [0.27-2.58]	cases	3/27	23/172
Kadnur	62%	0.38 [0.15-0.85]	cases	10/258	15/100
Khurana	51%	0.49 [0.24-0.98]	cases	6/22	88/159
Singer	-9%	1.09 [0.79-1.51]	cases	55/10,700	104/22,058
Salvarani	6%	0.94 [0.66-1.34]	cases	population-based cohort	
Ferri	63%	0.37 [0.16-0.83]	cases	9/994	16/647
de la Iglesia	-50%	1.50 [0.25-8.95]	hosp.	3/687	2/688
Laplana	-56%	1.56 [0.74-3.28]	cases	17/319	11/319
Rentsch	-3%	1.03 [0.80-1.33]	death	population-based cohort	
Grau-Pujol (RCT)	11%	0.89 [0.06-14.2]	cases	1/142	1/127
Rajasingham (RCT)	50%	0.50 [0.03-7.97]	hosp.	1/989	1/494
Gentry	91%	0.09 [0.00-1.52]	death	0/10,703	7/21,406
Abella (RCT)	5%	0.95 [0.25-3.63]	cases	4/64	4/61
Yadav	82%	0.18 [0.04-0.81]	hosp.	2/279	9/221
Goenka	87%	0.13 [0.02-0.85]	IgG+	1/77	115/885
Arleo	50%	0.50 [0.06-4.02]	death	1/20	5/50
Behera	28%	0.72 [0.32-1.24]	cases	7/19	179/353
Datta	22%	0.78 [0.42-1.45]	cases	16/146	19/135
Mathai	90%	0.10 [0.05-0.21]	cases	10/491	22/113
Revollo (PSM)	23%	0.77 [0.35-1.68]	cases	16/69	65/418
Jung	59%	0.41 [0.02-9.97]	death	0/649	1/1,417
Gönenli	30%	0.70 [0.20-2.46]	progression	3/148	12/416
Huh	-251%	3.51 [0.76-16.2]	progression	5/8	873/2,797
Cordtz	24%	0.76 [0.23-2.52]	hosp.	population-based cohort	
Rangel	25%	0.75 [0.25-2.24]	death	4/50	11/103
Khoubnasabjafari	17%	0.83 [0.44-1.59]	cases	34/1,436	12/422
Trefond	-17%	1.17 [0.33-3.54]	death	4/68	12/183
Fitzgerald	9%	0.91 [0.69-1.21]	cases	65/1,072	200/3,594
Mahto	27%	0.73 [0.33-1.33]	IgG+	9/89	84/600
Bae (PSM)	30%	0.70 [0.41-1.18]	cases	16/743	91/2,698
Pham	20%	0.80 [0.15-2.79]	death	2/14	5/28
Vivanco-Hidalgo	-46%	1.46 [0.91-2.34]	hosp.	40/6,746	50/13,492
Dev	26%	0.74 [0.61-0.90]	cases	260 (n)	499 (n)
Alegiani	-8%	1.08 [0.79-1.46]	death	case control	
Alzahrani	59%	0.41 [0.02-9.55]	death	0/14	1/33
Rojas-Serrano (RCT)	82%	0.18 [0.02-1.59]	symp. case	1/62	6/65
Syed (RCT)	-60%	1.60 [0.63-4.04]	symp. case	10/48	6/46
Kamstrup	-44%	1.44 [0.78-2.65]	hosp.	population-based cohort	
Korkmaz	82%	0.18 [0.01-3.72]	death	0/385	2/299
Badyal	60%	0.40 [0.31-0.50]	cases	247/617	611/1,473
Shaw (PSM)	13%	0.87 [0.80-0.96]	cases	45 (n)	99 (n)
Küçükakkaş	-43%	1.43 [0.11-19.2]	ICU	1/7	1/10
Bhatt	-49%	1.49 [1.05-2.13]	cases	167/731	30/196
Patil	66%	0.34 [0.10-1.22]	death	5,266 (n)	3,946 (n)
Naggie (RCT)	24%	0.76 [0.51-1.14]	symp. case	41/683	53/676
Cordtz	40%	0.60 [0.19-1.87]	hosp.	1,170 (n)	1,363 (n)
Agarwal	95%	0.05 [0.00-0.85]	hosp.	0/29	17/455
Fung	13%	0.87 [0.72-1.05]	death	population-based cohort	
Belmont	79%	0.21 [0.02-2.25]	symp. case	1/56	2/24
Samajdar	75%	0.25 [0.14-0.47]	cases	12/129	29/81
Ahmed	99%	0.01 [0.00-0.11]	cases	case control	
Rao	11%	0.89 [0.53-1.52]	cases	16/273	67/1,021
McKinnon (RCT)	2%	0.98 [0.09-10.7]	symp. case	2/365	1/178
Juneja	-142%	2.42 [0.22-26.6]	severe case	2/996	1/1,204
Erden	-150%	2.50 [0.13-48.0]	death	1/6	0/3
Ugarte-Gil	44%	0.56 [0.36-0.85]	severe case	665 (n)	230 (n)
Opdam	45%	0.55 [0.23-1.30]	hosp.	case control	
Del Amo (RCT)	51%	0.49 [0.00-2.29]	symp. case	3/231	5/223
Oztas	-215%	3.15 [0.33-30.1]	hosp.	3/317	1/333
MacFadden	12%	0.88 [0.79-0.97]	cases	n/a	n/a
Satti	61%	0.39 [0.17-0.86]	cases	10/63	7/17
PrEP	31%	0.69 [0.59-0.79]		984/50,357	4,695/103,891

31% improvement

$Tau^2 = 0.18$, $I^2 = 82.4\%$, $p < 0.0001$

	Improvement, RR [CI]			*Treatment*	*Control*
Boulware (RCT)	17%	0.83 [0.58-1.18]	cases	49/414	58/407
Mitjà (RCT)	46%	0.54 [0.16-1.80]	death	4/1,196	8/1,301
Polat	57%	0.43 [0.21-0.88]	cases	12/138	14/70



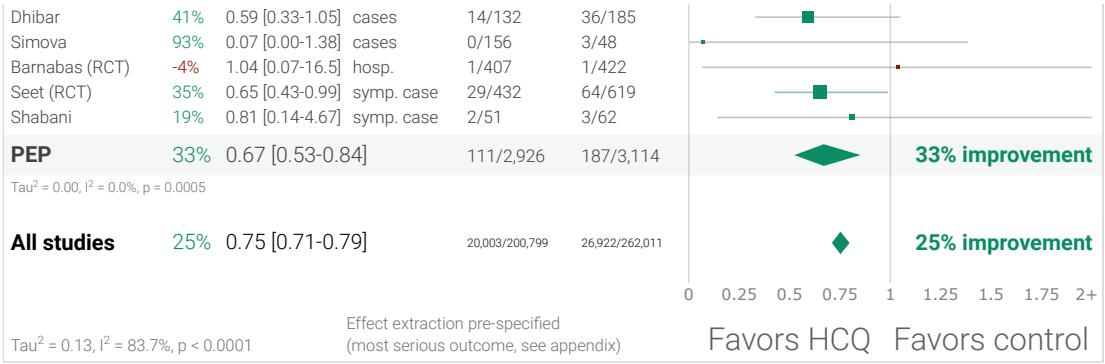


Figure 6. *Random effects meta-analysis. This plot shows pooled effects, analysis for individual outcomes is below, and more details on pooled effects can be found in the heterogeneity section. Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details. (ES) indicates the early treatment subset of a study (these are not included in the overall results).*

All 216 HCQ COVID-19 mortality results

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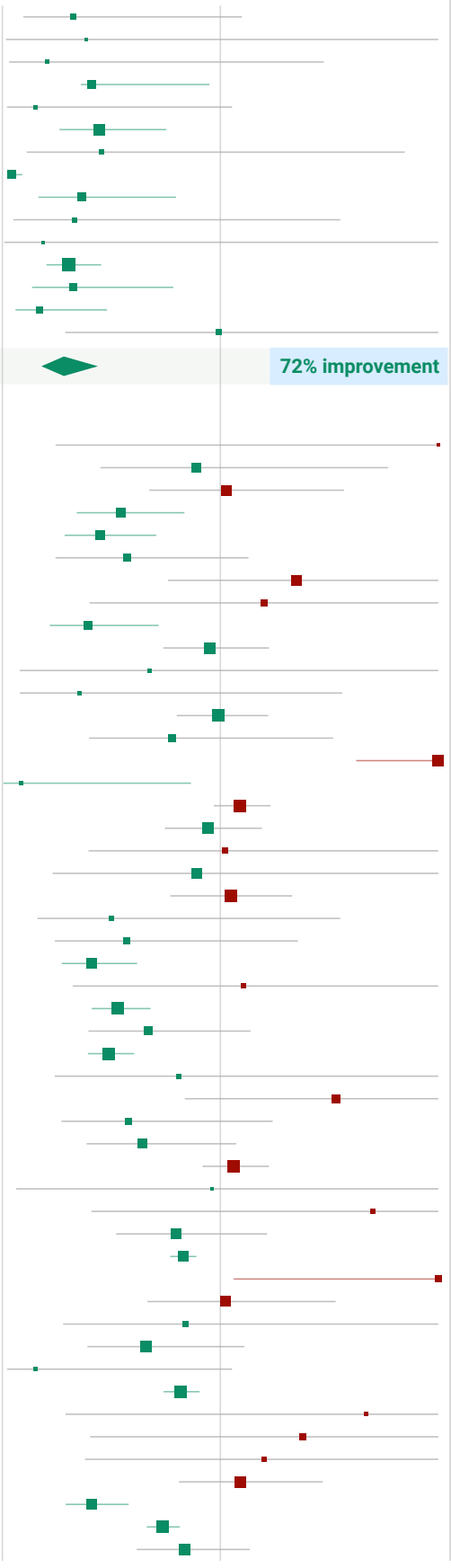
	Improvement, RR [CI]		Treatment	Control
Ashraf	68%	0.32 [0.10-1.10]	10/77	2/5
Guérin	61%	0.39 [0.02-9.06]	0/20	1/34
Derwand	79%	0.21 [0.03-1.47]	1/141	13/377
Bernabeu-Wittel	59%	0.41 [0.36-0.95]	189 (n)	83 (n)
Yu (ES)	85%	0.15 [0.02-1.05]	1/73	238/2,604
Ly	56%	0.44 [0.26-0.75]	18/116	29/110
Ip	55%	0.45 [0.11-1.85]	2/97	44/970
Heras	96%	0.04 [0.02-0.09]	8/70	16/30
Sulaiman	64%	0.36 [0.17-0.80]	7/1,817	54/3,724
Guisado-Vasco (ES)	67%	0.33 [0.05-1.55]	2/65	139/542
Cadegiani	81%	0.19 [0.01-3.88]	0/159	2/137
Mokhtari	70%	0.30 [0.20-0.45]	27/7,295	287/21,464
Corradini (ES)	67%	0.33 [0.14-0.78]	641 (n)	102 (n)
Million	83%	0.17 [0.06-0.48]	5/8,315	11/2,114
Avezum (RCT)	1%	0.99 [0.29-3.41]	5/687	5/682
Early treatment	72%	0.28 [0.19-0.43]	86/19,762	841/32,978

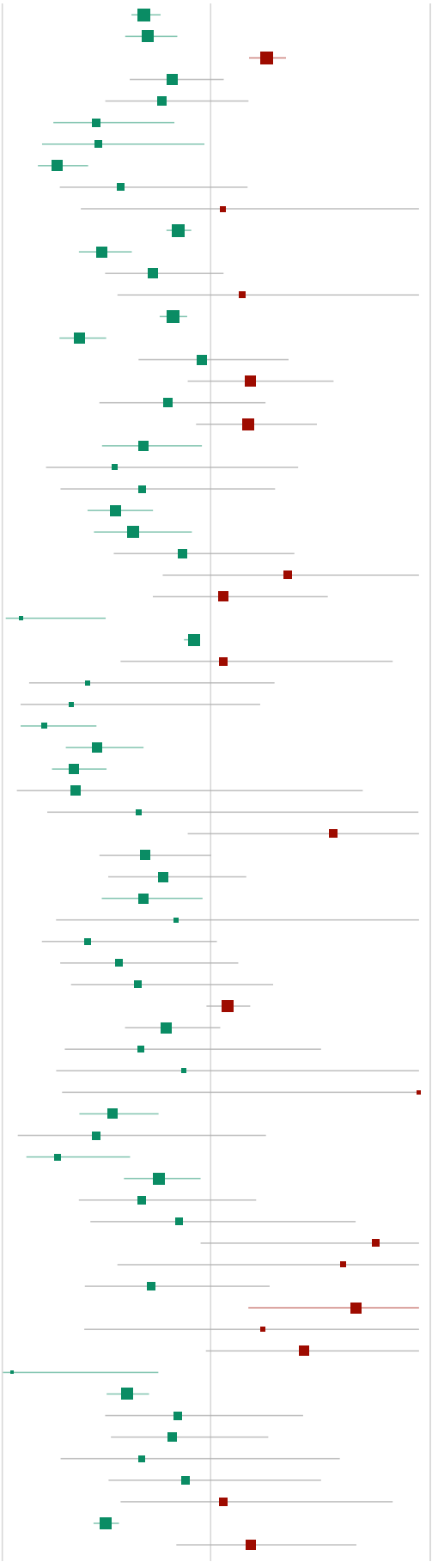
72% improvement

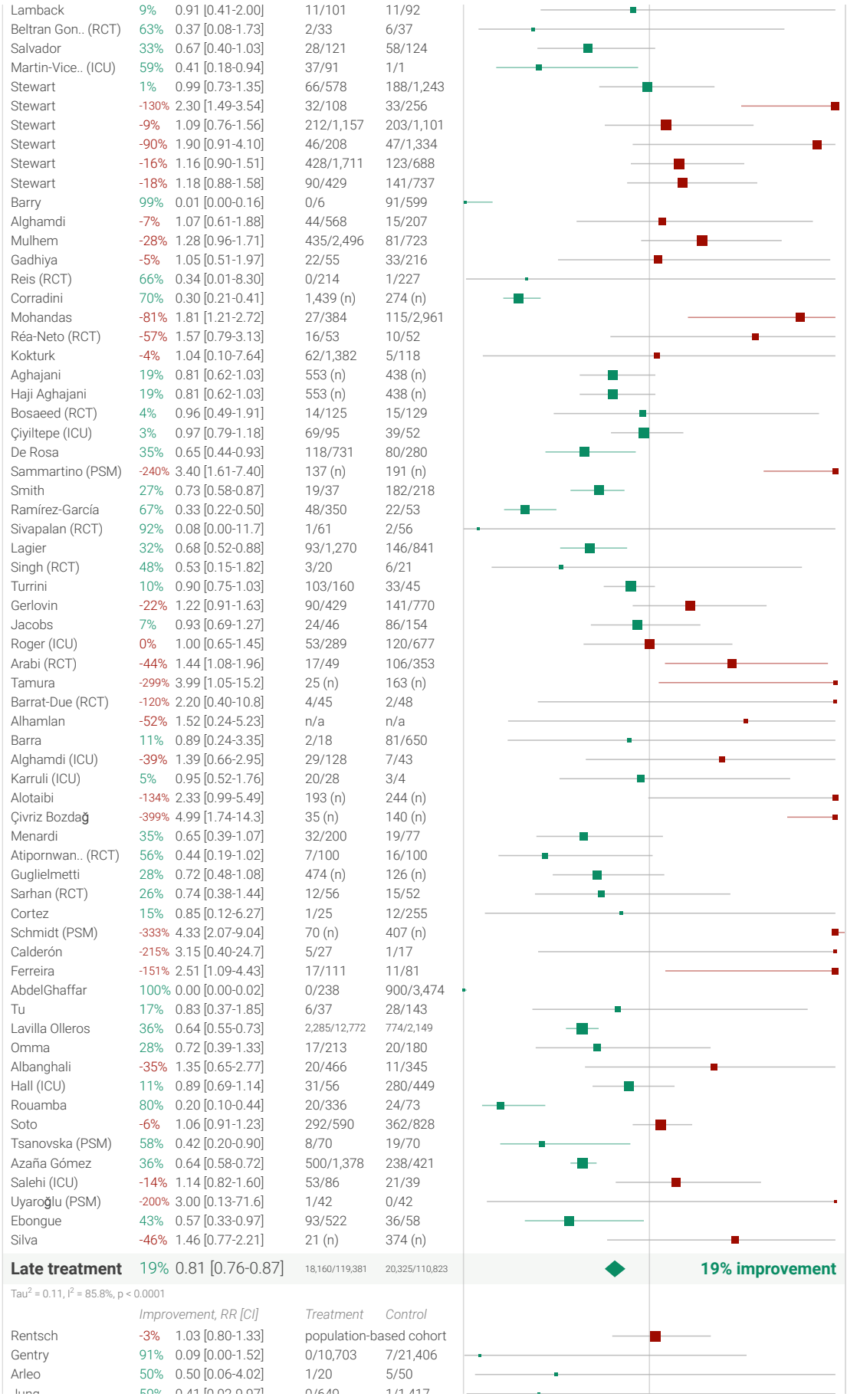
$Tau^2 = 0.32$, $I^2 = 60.0\%$, $p < 0.0001$

	Improvement, RR [CI]		Treatment	Control
Barbosa	-147%	2.47 [0.24-25.0]	2/17	1/21
Magagnoli	11%	0.89 [0.45-1.77]	39/148	18/163
Auld	-3%	1.03 [0.67-1.57]	33/114	29/103
Sánchez-Álvarez	46%	0.54 [0.34-0.84]	322 (n)	53 (n)
Membrillo de No..	55%	0.45 [0.29-0.71]	27/123	21/43
Alberici	43%	0.57 [0.24-1.13]	17/72	9/22
Rosenberg	-35%	1.35 [0.76-2.40]	189/735	28/221
Mahévas	-20%	1.20 [0.40-3.30]	9/84	8/89
Yu	60%	0.40 [0.22-0.72]	9/48	238/502
Singh	5%	0.95 [0.74-1.22]	104/910	109/910
Luo	32%	0.68 [0.08-5.88]	19 (n)	264 (n)
Hraiech (ICU)	65%	0.35 [0.08-1.56]	2/17	5/15
Ip	1%	0.99 [0.80-1.22]	432/1,914	115/598
Goldman	22%	0.78 [0.40-1.52]	10/109	34/288
Kuderer	-134%	2.34 [1.62-3.21]	45/181	121/928
Rogado	92%	0.08 [0.00-0.87]	1/8	7/9
RECOVERY (RCT)	-9%	1.09 [0.97-1.23]	421/1,561	790/3,155
Wang	6%	0.94 [0.75-1.19]	1,866 (n)	5,726 (n)
Luo	-2%	1.02 [0.39-2.65]	11/35	4/13
Paccoud	11%	0.89 [0.23-3.47]	21/38	26/46
Sbidian	-5%	1.05 [0.77-1.33]	111/623	830/3,792
Fontana	50%	0.50 [0.16-1.55]	4/12	2/3
Bousquet	43%	0.57 [0.24-1.36]	5/27	23/81
Lagier	59%	0.41 [0.27-0.62]	35/3,119	58/618
Sosa-García (ICU)	-11%	1.11 [0.32-3.78]	7/38	3/18
Mikami	47%	0.53 [0.41-0.68]	575/2,077	231/743
Martinez-Lopez	33%	0.67 [0.39-1.14]	47/148	9/19
Arshad	51%	0.49 [0.39-0.60]	162/1,202	108/409
Rivera-Izquierdo	19%	0.81 [0.24-2.76]	215 (n)	23 (n)
Cravedi	-53%	1.53 [0.84-2.80]	36/101	10/43
Lecronier (ICU)	42%	0.58 [0.27-1.24]	9/38	9/22
Trullàs	36%	0.64 [0.39-1.07]	20/66	16/34
Gupta	-6%	1.06 [0.92-1.22]	631/1,761	153/454
Lyngbakken (RCT)	4%	0.96 [0.06-14.6]	1/27	1/26
McGrail	-70%	1.70 [0.41-7.07]	4/33	3/42
Krishnan	20%	0.80 [0.52-1.21]	86/144	6/8
Bernaola	17%	0.83 [0.77-0.89]	236/1,498	28/147
Kelly	-143%	2.43 [1.06-5.56]	23/82	6/52
Rivera	-2%	1.02 [0.67-1.53]	44/179	59/327
Cavalcanti (RCT)	16%	0.84 [0.28-2.53]	8/331	5/173
D'Arminio Monfo..	34%	0.66 [0.39-1.11]	53/197	47/92
Yu	85%	0.15 [0.02-1.05]	1/73	238/2,604
Berenguer	18%	0.82 [0.74-0.90]	681/2,618	438/1,377
Kalligeros	-67%	1.67 [0.29-9.36]	36 (n)	72 (n)
Roomi	-38%	1.38 [0.40-2.76]	13/144	6/32
Abd-Elsalam (RCT)	-20%	1.20 [0.38-3.80]	6/97	5/97
Peters	-9%	1.09 [0.81-1.47]	419/1,596	53/353
Pinato	59%	0.41 [0.29-0.58]	30/182	181/446
Gonzalez	27%	0.73 [0.66-0.81]	1,246/8,476	341/1,168
Pasquini (ICU)	16%	0.84 [0.62-1.14]	23/33	15/18



Catteau	32%	0.68 [0.62-0.76]	804/4,542	957/3,533
Di Castelnuovo	30%	0.70 [0.59-0.84]	386/2,634	90/817
Fried	-27%	1.27 [1.18-1.36]	1,048/4,232	1,466/7,489
Albani	18%	0.82 [0.61-1.06]	60/211	172/605
Synolaki	24%	0.76 [0.49-1.18]	21/98	60/214
Alamdari	55%	0.45 [0.25-0.83]	54/427	9/32
Heberto	54%	0.46 [0.19-0.97]	139 (n)	115 (n)
Lauriola	74%	0.27 [0.17-0.41]	102/297	35/63
Serrano	43%	0.57 [0.28-1.18]	6/14	6/8
Ulrich (RCT)	-6%	1.06 [0.38-2.98]	7/67	6/61
Shoaibi	15%	0.85 [0.79-0.91]	686/5,047	3,923/24,404
Ayerbe	52%	0.48 [0.37-0.62]	237/1,857	49/162
Nachega	28%	0.72 [0.49-1.06]	69/630	28/96
Ader (RCT)	-15%	1.15 [0.55-2.27]	11/150	13/149
Soto-Becerra	18%	0.82 [0.76-0.89]	346/692	1,606/2,630
Aparisi	63%	0.37 [0.27-0.50]	122/605	27/49
Annie	4%	0.96 [0.65-1.37]	48/367	50/367
SOLIDARITY (RCT)	-19%	1.19 [0.89-1.59]	104/947	84/906
Guisado-Vasco	20%	0.80 [0.47-1.26]	127/558	14/49
Solh	-18%	1.18 [0.93-1.51]	131/265	134/378
Ñamendys-S.. (ICU)	32%	0.68 [0.48-0.96]	24/54	42/64
Dubee (RCT)	46%	0.54 [0.21-1.42]	6/124	11/123
Lano	33%	0.67 [0.28-1.31]	56 (n)	66 (n)
Coll	46%	0.54 [0.41-0.72]	55/307	108/328
Frontera (PSM)	37%	0.63 [0.44-0.91]	121/1,006	424/2,467
Tehrani	13%	0.87 [0.54-1.40]	16/65	54/190
Salazar	-37%	1.37 [0.77-2.42]	12/92	80/811
Rodriguez-Nava	-6%	1.06 [0.72-1.56]	22/65	79/248
Maldonado	91%	0.09 [0.02-0.50]	1/11	1/1
Núñez-Gil	8%	0.92 [0.87-0.94]	200/686	100/268
Self (RCT)	-6%	1.06 [0.57-1.87]	25/241	25/236
Rodriguez	59%	0.41 [0.13-1.31]	8/39	2/4
Águila-Gordo	67%	0.33 [0.09-1.24]	151/346	47/70
Sheshah	80%	0.20 [0.09-0.45]	267 (n)	33 (n)
Boari	55%	0.45 [0.30-0.68]	41/202	25/56
Budhiraja	65%	0.35 [0.24-0.50]	69/834	34/142
Falcone (PSM)	65%	0.35 [0.07-1.73]	40/238	30/77
Qin	34%	0.66 [0.22-2.00]	3/43	75/706
Burdick	-59%	1.59 [0.89-2.83]	142 (n)	148 (n)
van Halem	32%	0.68 [0.47-1.00]	34/164	47/155
Rodriguez-Gonzalez	23%	0.77 [0.51-1.17]	251/1,148	17/60
Lambermont	32%	0.68 [0.48-0.96]	97/225	14/22
Abdulrahman (PSM)	17%	0.83 [0.26-2.69]	5/223	6/223
Modrák	59%	0.41 [0.19-1.03]	108 (n)	105 (n)
Ozturk	44%	0.56 [0.28-1.13]	165/1,127	6/23
Guglielmetti	35%	0.65 [0.33-1.30]	181 (n)	37 (n)
Rosenthal	-8%	1.08 [0.98-1.19]	n/a	n/a
Bielza	22%	0.78 [0.59-1.05]	33/91	249/539
Naseem	33%	0.67 [0.30-1.53]	77 (n)	1,137 (n)
Orioli	13%	0.87 [0.26-2.94]	8/55	3/18
De Luna	-105%	2.05 [0.29-14.6]	15/132	1/18
Signes-Costa	47%	0.53 [0.37-0.75]	4,854 (n)	993 (n)
Matangila	55%	0.45 [0.07-1.27]	25/147	8/13
Cangiano	73%	0.27 [0.12-0.61]	5/33	37/65
Taccone (ICU)	25%	0.75 [0.58-0.95]	449/1,308	183/439
Chari	33%	0.67 [0.37-1.22]	8/29	195/473
Vernaz (PSM)	15%	0.85 [0.42-1.70]	12/93	16/105
Texeira	-79%	1.79 [0.95-3.38]	17/65	14/96
Psevdos	-63%	1.63 [0.55-4.84]	17/52	3/15
Mahale	29%	0.71 [0.40-1.28]	25/102	11/32
Sands	-70%	1.70 [1.18-2.42]	101/973	56/696
Lotfy	-25%	1.25 [0.39-3.96]	6/99	5/103
Sarfaraz	-45%	1.45 [0.98-2.15]	40/94	27/92
Yegerov	95%	0.05 [0.00-0.75]	0/23	20/1,049
Di Castelnuovo	40%	0.60 [0.50-0.70]	3,270 (n)	1,000 (n)
Roig	16%	0.84 [0.49-1.44]	33/67	7/12
Ubaldo (ICU)	18%	0.82 [0.52-1.28]	17/25	5/6
Ouedraogo	33%	0.67 [0.28-1.62]	397 (n)	59 (n)
Hernandez-C.. (RCT)	12%	0.88 [0.51-1.53]	106 (n)	108 (n)
Thompson (RCT)	-6%	1.06 [0.57-1.87]	25/241	25/236
Lora-Tamayo	50%	0.50 [0.44-0.56]	7,192 (n)	1,361 (n)
Awad	-19%	1.19 [0.84-1.70]	56/188	37/148




Lamback 9% 0.91 [0.41-2.00] 11/101 11/92
Beltran Gon.. (RCT) 63% 0.37 [0.08-1.73] 2/33 6/37
Salvador 33% 0.67 [0.40-1.03] 28/121 58/124
Martin-Vice.. (ICU) 59% 0.41 [0.18-0.94] 37/91 1/1
Stewart 1% 0.99 [0.73-1.35] 66/578 188/1,243
Stewart -130% 2.30 [1.49-3.54] 32/108 33/256
Stewart -9% 1.09 [0.76-1.56] 212/1,157 203/1,101
Stewart -90% 1.90 [0.91-4.10] 46/208 47/1,334
Stewart -16% 1.16 [0.90-1.51] 428/1,711 123/688
Stewart -18% 1.18 [0.88-1.58] 90/429 141/737
Barry 99% 0.01 [0.00-0.16] 0/6 91/599
Alghamdi -7% 1.07 [0.61-1.88] 44/568 15/207
Mulhem -28% 1.28 [0.96-1.71] 435/2,496 81/723
Gadhiya -5% 1.05 [0.51-1.97] 22/55 33/216
Reis (RCT) 66% 0.34 [0.01-8.30] 0/214 1/227
Corradini 70% 0.30 [0.21-0.41] 1,439 (n) 274 (n)
Mohandas -81% 1.81 [1.21-2.72] 27/384 115/2,961
Réa-Neto (RCT) -57% 1.57 [0.79-3.13] 16/53 10/52
Kokturk -4% 1.04 [0.10-7.64] 62/1,382 5/118
Aghajani 19% 0.81 [0.62-1.03] 553 (n) 438 (n)
Haji Aghajani 19% 0.81 [0.62-1.03] 553 (n) 438 (n)
Bosaeed (RCT) 4% 0.96 [0.49-1.91] 14/125 15/129
Çiyiltepe (ICU) 3% 0.97 [0.79-1.18] 69/95 39/52
De Rosa 35% 0.65 [0.44-0.93] 118/731 80/280
Sammartino (PSM) -240% 3.40 [1.61-7.40] 137 (n) 191 (n)
Smith 27% 0.73 [0.58-0.87] 19/37 182/218
Ramírez-García 67% 0.33 [0.22-0.50] 48/350 22/53
Sivapalan (RCT) 92% 0.08 [0.00-11.7] 1/61 2/56
Lagier 32% 0.68 [0.52-0.88] 93/1,270 146/841
Singh (RCT) 48% 0.53 [0.15-1.82] 3/20 6/21
Turrini 10% 0.90 [0.75-1.03] 103/160 33/45
Gerlovin -22% 1.22 [0.91-1.63] 90/429 141/770
Jacobs 7% 0.93 [0.69-1.27] 24/46 86/154
Roger (ICU) 0% 1.00 [0.65-1.45] 53/289 120/677
Arabi (RCT) -44% 1.44 [1.08-1.96] 17/49 106/353
Tamura -299% 3.99 [1.05-15.2] 25 (n) 163 (n)
Barrat-Due (RCT) -120% 2.20 [0.40-10.8] 4/45 2/48
Alhamlan -52% 1.52 [0.24-5.23] n/a n/a
Barra 11% 0.89 [0.24-3.35] 2/18 81/650
Alghamdi (ICU) -39% 1.39 [0.66-2.95] 29/128 7/43
Karruli (ICU) 5% 0.95 [0.52-1.76] 20/28 3/4
Alotaibi -134% 2.33 [0.99-5.49] 193 (n) 244 (n)
Çivriz Bozdağ -399% 4.99 [1.74-14.3] 35 (n) 140 (n)
Menardi 35% 0.65 [0.39-1.07] 32/200 19/77
Atipornwan.. (RCT) 56% 0.44 [0.19-1.02] 7/100 16/100
Guglielmetti 28% 0.72 [0.48-1.08] 474 (n) 126 (n)
Sarhan (RCT) 26% 0.74 [0.38-1.44] 12/56 15/52
Cortez 15% 0.85 [0.12-6.27] 1/25 12/255
Schmidt (PSM) -333% 4.33 [2.07-9.04] 70 (n) 407 (n)
Calderón -215% 3.15 [0.40-24.7] 5/27 1/17
Ferreira -151% 2.51 [1.09-4.43] 17/111 11/81
AbdelGhaffar 100% 0.00 [0.00-0.02] 0/238 900/3,474
Tu 17% 0.83 [0.37-1.85] 6/37 28/143
Lavilla Olleros 36% 0.64 [0.55-0.73] 2,285/12,772 774/2,149
Omma 28% 0.72 [0.39-1.33] 17/213 20/180
Albanghali -35% 1.35 [0.65-2.77] 20/466 11/345
Hall (ICU) 11% 0.89 [0.69-1.14] 31/56 280/449
Rouamba 80% 0.20 [0.10-0.44] 20/336 24/73
Soto -6% 1.06 [0.91-1.23] 292/590 362/828
Tsanovska (PSM) 58% 0.42 [0.20-0.90] 8/70 19/70
Azaña Gómez 36% 0.64 [0.58-0.72] 500/1,378 238/421
Salehi (ICU) -14% 1.14 [0.82-1.60] 53/86 21/39
Uyaroğlu (PSM) -200% 3.00 [0.13-71.6] 1/42 0/42
Ebongue 43% 0.57 [0.33-0.97] 93/522 36/58
Silva -46% 1.46 [0.77-2.21] 21 (n) 374 (n)
Late treatment 19% 0.81 [0.76-0.87] 18,160/119,381 20,325/110,823
19% improvement
Tau² = 0.11, I² = 85.8%, p < 0.0001
Improvement, RR [CI] Treatment Control
Rentsch -3% 1.03 [0.80-1.33] population-based cohort
Gentry 91% 0.09 [0.00-1.52] 0/10,703 7/21,406
Arleo 50% 0.50 [0.06-4.02] 1/20 5/50

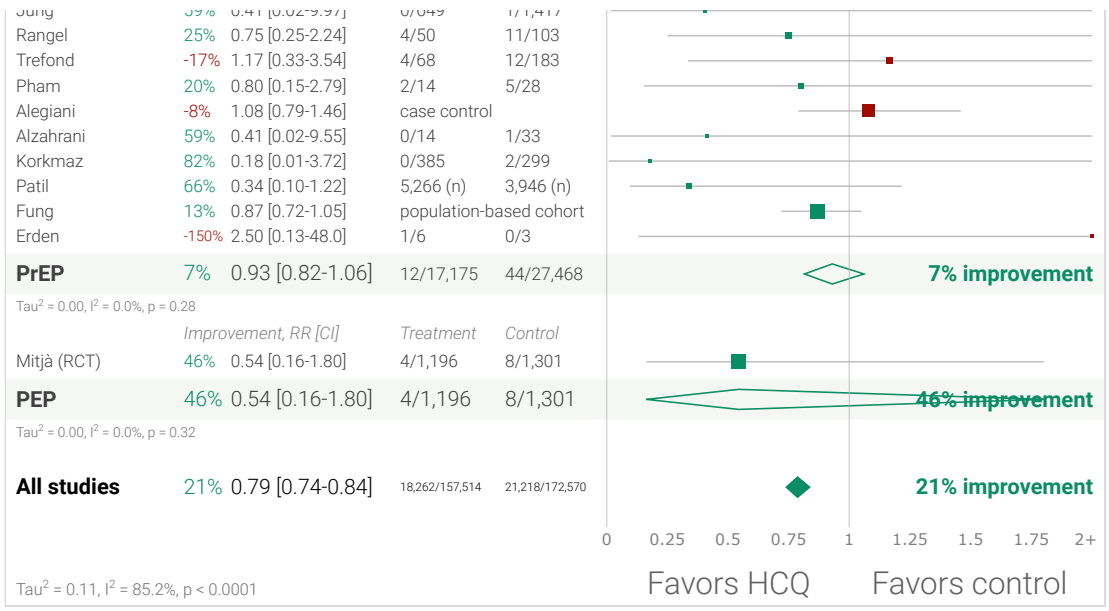


Figure 7. *Random effects meta-analysis for mortality results only. (ES) indicates the early treatment subset of a study (these are not included in the overall results).*

All 51 HCQ COVID-19 hospitalization results

hcqmeta.com Jun 2022

	Improvement	RR [CI]		Treatment	Control
Esper	64%	0.36 [0.15-0.87]	hosp.	8/412	12/224
Derwand	82%	0.18 [0.07-0.54]	hosp.	4/141	58/377
Mitjà (RCT)	16%	0.84 [0.35-2.03]	hosp.	8/136	11/157
Skipper (RCT)	49%	0.51 [0.15-1.66]	hosp.	4/231	8/234
Ip	37%	0.63 [0.37-0.96]	hosp.	21/97	305/970
Sulaiman	39%	0.61 [0.52-0.72]	hosp.	171/1,817	617/3,724
Szente Fonseca	64%	0.36 [0.20-0.67]	hosp.	25/175	89/542
Cadegiani	98%	0.02 [0.00-0.27]	hosp.	0/159	27/137
Simova	94%	0.06 [0.00-1.13]	hosp.	0/33	2/5
Omrani (RCT)	12%	0.88 [0.26-2.94]	hosp.	7/304	4/152
Mokhtari	35%	0.65 [0.59-0.71]	hosp.	523/7,295	2,382/21,464
Million	4%	0.96 [0.71-1.29]	hosp.	214/8,315	64/2,114
Rodrigues (RCT)	-200%	3.00 [0.13-71.6]	hosp.	1/42	0/42
Chechter	95%	0.05 [0.00-0.96]	hosp.	0/60	3/12
Avezum (RCT)	23%	0.77 [0.52-1.12]	hosp.	44/689	57/683
Early treatment	41%	0.59 [0.48-0.72]		1,030/19,906	3,639/30,837

41% improvement

$Tau^2 = 0.05$, $I^2 = 63.5\%$, $p < 0.0001$

	Improvement	RR [CI]		Treatment	Control
Kim	51%	0.49 [0.28-0.87]	hosp. time	22 (n)	40 (n)
Cavalcanti (RCT)	-28%	1.28 [0.81-2.03]	hosp.	331 (n)	173 (n)
Ashinyo	33%	0.67 [0.47-0.96]	hosp. time	61 (n)	61 (n)
Johnston (RCT)	30%	0.70 [0.19-2.54]	hosp.	5/148	4/83
Alqassieh	18%	0.82 [0.64-1.05]	hosp. time	63 (n)	68 (n)
Tan	35%	0.65 [0.43-0.98]	hosp. time	8 (n)	277 (n)
Vernaz (PSM)	-49%	1.49 [1.16-1.92]	hosp. time	93 (n)	105 (n)
Reis (RCT)	24%	0.76 [0.30-1.88]	hosp.	8/214	11/227
Bosaeed (RCT)	-12%	1.12 [0.85-1.49]	hosp. time	125 (n)	129 (n)
Schwartz (RCT)	-533%	6.33 [0.35-115]	hosp.	4/111	0/37
Sarhan (RCT)	-25%	1.25 [0.99-1.58]	hosp. time	56 (n)	52 (n)
Calderón	-107%	2.07 [1.23-3.51]	hosp. time	27 (n)	17 (n)
Omma	17%	0.83 [0.73-0.95]	hosp. time	213 (n)	180 (n)
Uyaroğlu (PSM)	10%	0.90 [0.20-4.14]	hosp. time	42 (n)	42 (n)
Hong (PSM)	-13%	1.13 [0.54-2.37]	hosp.	15 (n)	15 (n)
Late treatment	2%	0.98 [0.81-1.19]		17/1,529	15/1,506

2% improvement

$Tau^2 = 0.08$, $I^2 = 71.2\%$, $p = 0.87$

	Improvement	RR [CI]		Treatment	Control
Konig	3%	0.97 [0.65-1.46]	hosp.	16/29	29/51
Macias	26%	0.74 [0.07-8.18]	hosp.	1/290	2/432
Gianfrancesco	3%	0.97 [0.71-1.24]	hosp.	58/130	219/470
Huang	80%	0.20 [0.08-0.52]	hosp.	8 (n)	1,247 (n)
de la Iglesia	-50%	1.50 [0.25-8.95]	hosp.	3/687	2/688
Rajasingham (RCT)	50%	0.50 [0.03-7.97]	hosp.	1/989	1/494
Yadav	82%	0.18 [0.04-0.81]	hosp.	2/279	9/221
Cordtz	24%	0.76 [0.23-2.52]	hosp.	population-based cohort	
Rangel	22%	0.78 [0.50-1.21]	hosp.	17/50	45/103
Trefond	-45%	1.45 [0.89-2.08]	hosp.	24/71	53/191
Vivanco-Hidalgo	-46%	1.46 [0.91-2.34]	hosp.	40/6,746	50/13,492
Alegiani	18%	0.82 [0.69-0.98]	hosp.	case control	
Kamstrup	-44%	1.44 [0.78-2.65]	hosp.	population-based cohort	
Cordtz	40%	0.60 [0.19-1.87]	hosp.	1,170 (n)	1,363 (n)
Agarwal	95%	0.05 [0.00-0.85]	hosp.	0/29	17/455
Fung	3%	0.97 [0.86-1.09]	hosp.	population-based cohort	
Erden	75%	0.25 [0.04-1.77]	hosp.	1/6	2/3
Opdam	45%	0.55 [0.23-1.30]	hosp.	case control	
Oztas	-215%	3.15 [0.33-30.1]	hosp.	3/317	1/333
PrEP	10%	0.90 [0.76-1.08]		166/10,801	430/19,543

10% improvement

$Tau^2 = 0.05$, $I^2 = 54.3\%$, $p = 0.26$

	Improvement	RR [CI]		Treatment	Control
Mitjà (RCT)	17%	0.83 [0.41-1.71]	hosp.	13/1,196	17/1,301
Barnabas (RCT)	-4%	1.04 [0.07-16.5]	hosp.	1/407	1/422
PEP	16%	0.84 [0.42-1.69]		14/1,603	18/1,723

16% improvement

$Tau^2 = 0.00$, $I^2 = 0.0\%$, $p = 0.64$

All studies	18%	0.82 [0.72-0.92]		1,227/33,839	4,102/53,609

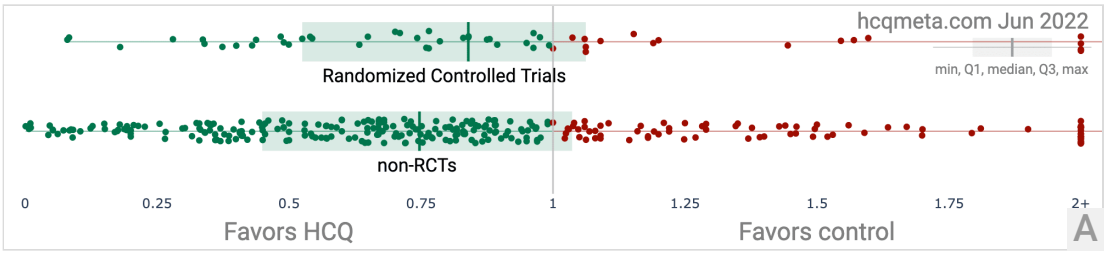
18% improvement

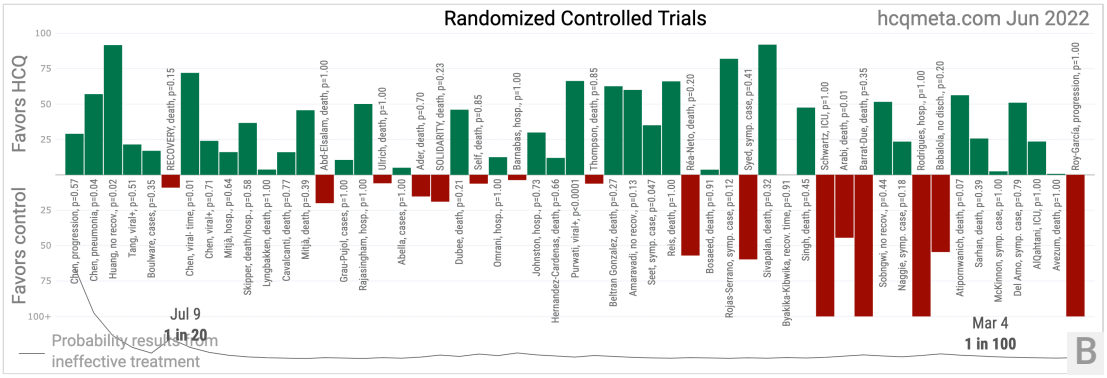
Figure 8. *Random effects meta-analysis for hospitalization results only.*

Randomized Controlled Trials (RCTs)

Randomized Controlled Trials (RCTs) minimize one source of bias and can provide a higher level of evidence. Results restricted to RCTs are shown in Figure 9, Figure 10, and Table 2. Even with the small number of RCTs to date, they confirm efficacy for early treatment. While late treatment RCTs are dominated by the very late stage and large RECOVERY/SOLIDARITY trials, prophylaxis and early treatment studies show 27% improvement in random effects meta-analysis, RR 0.73 [0.61-0.88], p = 0.00079. Early treatment RCTs show 39% improvement, RR 0.61 [0.41-0.92], p = 0.018.

Evidence supports incorporating non-RCT studies. ***[Concato]*** find that well-designed observational studies do not systematically overestimate the magnitude of the effects of treatment compared to RCTs. ***[Anglemyer]*** summarized reviews comparing RCTs to observational studies and found little evidence for significant differences in effect estimates. ***[Lee]*** shows that only 14% of the guidelines of the Infectious Diseases Society of America were based on RCTs. Limitations in an RCT can easily outweigh the benefits, for example excessive dosages, excessive treatment delays, or Internet survey bias could easily have a greater effect on results. Ethical issues may prevent running RCTs for known effective treatments. For more on the problems with RCTs see ***[Deaton, Nichol]***.


hcqmeta.com Jun 2022
Randomized Controlled Trials
min, Q1, median, Q3, max
non-RCTs
0
0.25
0.5
0.75
1
1.25
1.5
1.75
2+
Favors HCQ
Favors control
A


Randomized Controlled Trials
hcqmeta.com Jun 2022
Favors HCQ
Favors control
Jul 9
1 in 20
Mar 4
1 in 100
Probability results from ineffective treatment
B

All 54 HCQ COVID-19 RCTs

hcqmeta.com Jun 2022

	Improvement	RR [CI]		Treatment	Control
Huang (RCT)	92%	0.08 [0.01-1.32]	no recov.	0/10	6/12
Chen (RCT)	72%	0.28 [0.11-0.74]	viral time	18 (n)	12 (n)
Mitjà (RCT)	16%	0.84 [0.35-2.03]	hosp.	8/136	11/157
Skipper (RCT)	37%	0.63 [0.21-1.91]	death/hosp.	5/231	8/234
Omrani (RCT)	12%	0.88 [0.26-2.94]	hosp.	7/304	4/152
Amaravadi (RCT)	60%	0.40 [0.13-1.28]	no recov.	3/15	6/12
Sobngwi (RCT)	52%	0.48 [0.09-2.58]	no recov.	2/95	4/92
Rodrigues (RCT)	-200%	3.00 [0.13-71.6]	hosp.	1/42	0/42
Atipornwan.. (RCT)	-150%	2.50 [0.10-59.6]	progression	1/60	0/30
Avezum (RCT)	1%	0.99 [0.29-3.41]	death	5/687	5/682
Roy-García (RCT)	-100%	2.00 [0.19-20.9]	progression	2/31	1/31
Early treatment	39%	0.61 [0.41-0.92]		34/1,629	45/1,456

39% improvement

$Tau^2 = 0.00$, $I^2 = 0.0\%$, $p = 0.018$

	Improvement	RR [CI]		Treatment	Control
Chen (RCT)	29%	0.71 [0.29-1.74]	progression	5/15	7/15
Chen (RCT)	57%	0.43 [0.19-0.97]	pneumonia	6/31	14/31
Tang (RCT)	21%	0.79 [0.38-1.62]	viral+	11/75	14/75
RECOVERY (RCT)	-9%	1.09 [0.97-1.23]	death	421/1,561	790/3,155
Chen (RCT)	24%	0.76 [0.20-2.84]	viral+	4/21	3/12
Lyngbakken (RCT)	4%	0.96 [0.06-14.6]	death	1/27	1/26
Cavalcanti (RCT)	16%	0.84 [0.28-2.53]	death	8/331	5/173
Abd-Elsalam (RCT)	-20%	1.20 [0.38-3.80]	death	6/97	5/97
Ulrich (RCT)	-6%	1.06 [0.38-2.98]	death	7/67	6/61
Ader (RCT)	-15%	1.15 [0.55-2.27]	death	11/150	13/149
SOLIDARITY (RCT)	-19%	1.19 [0.89-1.59]	death	104/947	84/906
Dubee (RCT)	46%	0.54 [0.21-1.42]	death	6/124	11/123
Self (RCT)	-6%	1.06 [0.57-1.87]	death	25/241	25/236
Johnston (RCT)	30%	0.70 [0.19-2.54]	hosp.	5/148	4/83
Hernandez-C.. (RCT)	12%	0.88 [0.51-1.53]	death	106 (n)	108 (n)
Purwati (RCT)	66%	0.34 [0.26-0.44]	viral+	38/121	111/119
Thompson (RCT)	-6%	1.06 [0.57-1.87]	death	25/241	25/236
Beltran Gon.. (RCT)	63%	0.37 [0.08-1.73]	death	2/33	6/37
Reis (RCT)	66%	0.34 [0.01-8.30]	death	0/214	1/227
Réa-Neto (RCT)	-57%	1.57 [0.79-3.13]	death	16/53	10/52
Bosaeed (RCT)	4%	0.96 [0.49-1.91]	death	14/125	15/129
Sivapalan (RCT)	92%	0.08 [0.00-11.7]	death	1/61	2/56
Byakika-Ki.. (RCT)	0%	1.00 [0.56-1.75]	recov. time	36 (n)	29 (n)
Singh (RCT)	48%	0.53 [0.15-1.82]	death	3/20	6/21
Schwartz (RCT)	-133%	2.33 [0.10-56.1]	ICU	1/111	0/37
Arabi (RCT)	-44%	1.44 [1.08-1.96]	death	17/49	106/353
Barrat-Due (RCT)	-120%	2.20 [0.40-10.8]	death	4/45	2/48
Babalola (RCT)	-55%	1.55 [0.88-2.72]	no disch.	17/30	11/30
Atipornwan.. (RCT)	56%	0.44 [0.19-1.02]	death	7/100	16/100
Sarhan (RCT)	26%	0.74 [0.38-1.44]	death	12/56	15/52
AlQahtani (RCT)	24%	0.76 [0.18-3.25]	ICU	3/51	4/52
Late treatment	13%	0.87 [0.70-1.06]		780/5,287	1,312/6,828

13% improvement

$Tau^2 = 0.15$, $I^2 = 68.4\%$, $p = 0.17$

	Improvement	RR [CI]		Treatment	Control
Grau-Pujol (RCT)	11%	0.89 [0.06-14.2]	cases	1/142	1/127
Rajasingham (RCT)	50%	0.50 [0.03-7.97]	hosp.	1/989	1/494
Abella (RCT)	5%	0.95 [0.25-3.63]	cases	4/64	4/61
Rojas-Serrano (RCT)	82%	0.18 [0.02-1.59]	symp. case	1/62	6/65
Syed (RCT)	-60%	1.60 [0.63-4.04]	symp. case	10/48	6/46
Naggie (RCT)	24%	0.76 [0.51-1.14]	symp. case	41/683	53/676
McKinnon (RCT)	2%	0.98 [0.09-10.7]	symp. case	2/365	1/178
Del Amo (RCT)	51%	0.49 [0.00-2.29]	symp. case	3/231	5/223
PrEP	20%	0.80 [0.58-1.11]		63/2,584	77/1,870

20% improvement

$Tau^2 = 0.00$, $I^2 = 0.0\%$, $p = 0.19$

	Improvement	RR [CI]		Treatment	Control
Boulware (RCT)	17%	0.83 [0.58-1.18]	cases	49/414	58/407
Mitjà (RCT)	46%	0.54 [0.16-1.80]	death	4/1,196	8/1,301
Barnabas (RCT)	-4%	1.04 [0.07-16.5]	hosp.	1/407	1/422
Seet (RCT)	35%	0.65 [0.43-0.99]	symp. case	29/432	64/619
PEP	26%	0.74 [0.57-0.96]		83/2,449	131/2,749

26% improvement

$Tau^2 = 0.00$, $I^2 = 0.0\%$, $p = 0.025$

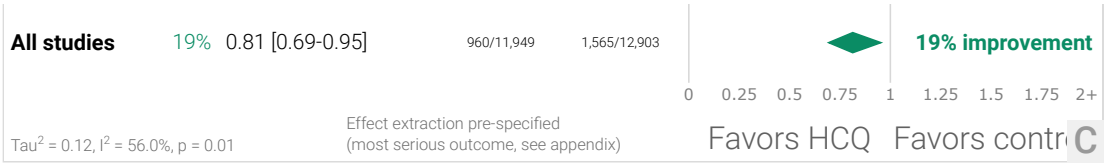
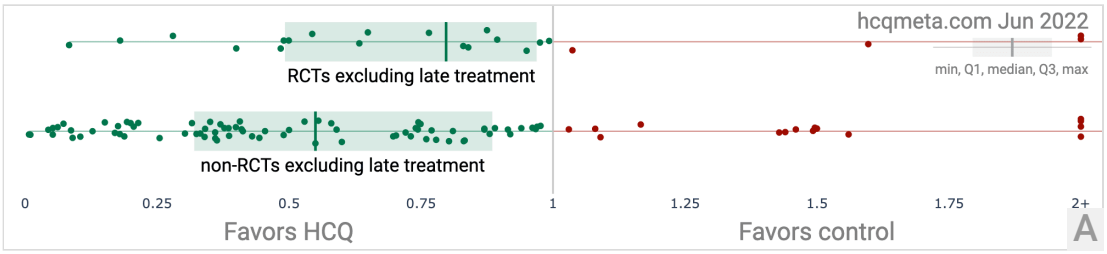
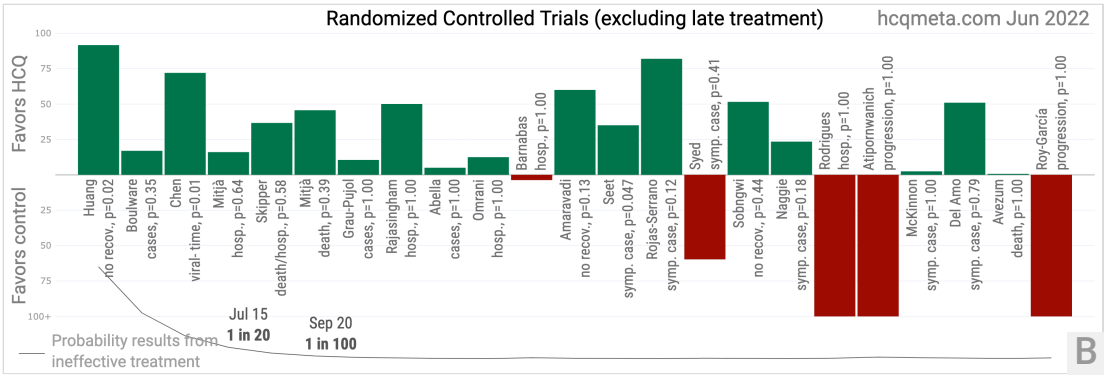


Figure 9. *Randomized Controlled Trials. Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details.* ***A.*** *Scatter plot of all effects comparing RCTs to non-RCTs.* ***B.*** *Chronological history of all reported effects.*





Hydroxychloroquine COVID-19 RCTs excluding late treatment

hcqmeta.com Jun 2022

	Improvement	RR [CI]		Treatment	Control
Huang (RCT)	92%	0.08 [0.01-1.32]	no recov.	0/10	6/12
Chen (RCT)	72%	0.28 [0.11-0.74]	viral time	18 (n)	12 (n)
Mitjà (RCT)	16%	0.84 [0.35-2.03]	hosp.	8/136	11/157
Skipper (RCT)	37%	0.63 [0.21-1.91]	death/hosp.	5/231	8/234
Omrani (RCT)	12%	0.88 [0.26-2.94]	hosp.	7/304	4/152
Amaravadi (RCT)	60%	0.40 [0.13-1.28]	no recov.	3/15	6/12
Sobngwi (RCT)	52%	0.48 [0.09-2.58]	no recov.	2/95	4/92
Rodrigues (RCT)	-200%	3.00 [0.13-71.6]	hosp.	1/42	0/42
Atipornwan.. (RCT)	-150%	2.50 [0.10-59.6]	progression	1/60	0/30
Avezum (RCT)	1%	0.99 [0.29-3.41]	death	5/687	5/682
Roy-García (RCT)	-100%	2.00 [0.19-20.9]	progression	2/31	1/31
Early treatment	39%	0.61 [0.41-0.92]		34/1,629	45/1,456

$Tau^2 = 0.00, I^2 = 0.0\%, p = 0.018$

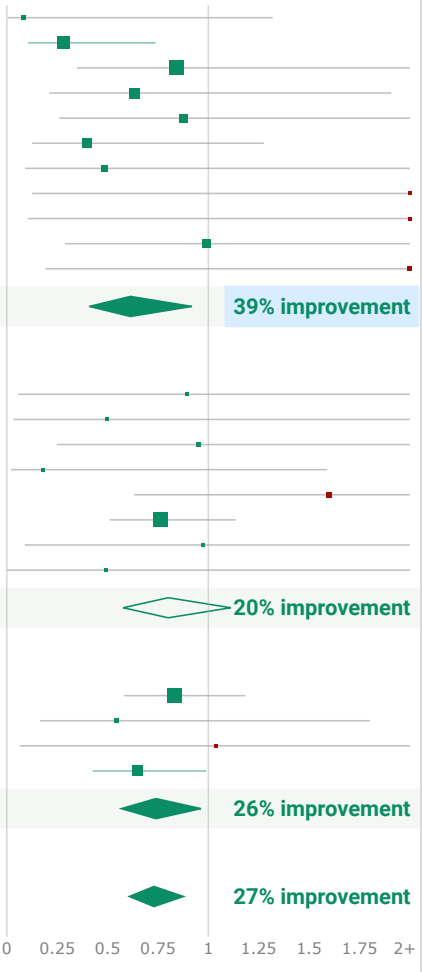
	Improvement	RR [CI]		Treatment	Control
Grau-Pujol (RCT)	11%	0.89 [0.06-14.2]	cases	1/142	1/127
Rajasingham (RCT)	50%	0.50 [0.03-7.97]	hosp.	1/989	1/494
Abella (RCT)	5%	0.95 [0.25-3.63]	cases	4/64	4/61
Rojas-Serrano (RCT)	82%	0.18 [0.02-1.59]	symp. case	1/62	6/65
Syed (RCT)	-60%	1.60 [0.63-4.04]	symp. case	10/48	6/46
Naggie (RCT)	24%	0.76 [0.51-1.14]	symp. case	41/683	53/676
McKinnon (RCT)	2%	0.98 [0.09-10.7]	symp. case	2/365	1/178
Del Amo (RCT)	51%	0.49 [0.00-2.29]	symp. case	3/231	5/223
PrEP	20%	0.80 [0.58-1.11]		63/2,584	77/1,870

$Tau^2 = 0.00, I^2 = 0.0\%, p = 0.19$

	Improvement	RR [CI]		Treatment	Control
Boulware (RCT)	17%	0.83 [0.58-1.18]	cases	49/414	58/407
Mitjà (RCT)	46%	0.54 [0.16-1.80]	death	4/1,196	8/1,301
Barnabas (RCT)	-4%	1.04 [0.07-16.5]	hosp.	1/407	1/422
Seet (RCT)	35%	0.65 [0.43-0.99]	symp. case	29/432	64/619
PEP	26%	0.74 [0.57-0.96]		83/2,449	131/2,749

$Tau^2 = 0.00, I^2 = 0.0\%, p = 0.025$

All studies	27%	0.73 [0.61-0.88]		180/6,662	253/6,075



$Tau^2 = 0.00, I^2 = 0.0\%, p = 0.00079$

Effect extraction pre-specified
(most serious outcome, see appendix)

C

Figure 10. *RCTs excluding late treatment. Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details.* ***A.*** *Scatter plot of all effects comparing RCTs to non-RCTs.* ***B.*** *Chronological history of all reported effects.* ***C.*** *Random effects meta-analysis.*

Treatment time	Number of studies reporting positive results	Total number of studies	Percentage of studies reporting positive results	Probability of an equal or greater percentage of positive results from an ineffective treatment	Random effects meta-analysis results
Randomized Controlled Trials	36	53	67.9%	1 in 158	19% improvement RR 0.81 [0.69-0.95] p = 0.01
Randomized Controlled Trials (excluding late treatment)	18	23	78.3%	1 in 188	27% improvement RR 0.73 [0.61-0.88] p = 0.00079

Table 2. *Summary of RCT results.*

Analysis with Exclusions

Many meta-analyses for HCQ have been written, most of which have become somewhat obselete due to the continuing stream of more recent studies. Recent analyses with positive conclusions include ***[IHU Marseille]*** which considers significant bias from an understanding of each trial, and ***[Garcia-Albeniz, Ladapo, Prodromos]*** which focus on early or prophylactic use studies.

Meta analyses reporting negative conclusions focus on late treatment studies, tend to disregard treatment delay, tend to follow formulaic evaluations which overlook major issues with various studies, and end up with weighting disproportionate to a reasoned analysis of each study's contribution. For example, ***[Axfors]*** assigns 87% weight to a single trial, the RECOVERY trial ***[RECOVERY]***, thereby producing the same result. However, the RECOVERY trial may be the most biased of the studies they included, due to the excessive dosage used, close to the level shown to be very dangerous in ***[Borba]*** (OR 2.8), and with extremely sick late stage patients (60% requiring oxygen, 17% ventilation/ECMO, and a very high mortality rate in both arms). There is little reason to suggest that the results from this trial are applicable to more typical dosages or to earlier treatment (10/22: the second version of this study released 10/22 assigns 74% to RECOVERY and 15% to SOLIDARITY ***[SOLIDARITY]***, which is the only other trial using a similar excessive dosage).

We include all studies in the main analysis, however there are major issues with several studies that could significantly alter the results. Here, we present an analysis excluding studies with significant issues, including indication of significant unadjusted group differences or confouding by indication, extremely late stage usage >14 days post symptoms or >50% on oxygen at baseline, very minimal detail provided, excessive dosages which have been shown to be dangerous, significant issues with adjustments that could reasonably make substantial differences, and reliance on PCR which may be inaccurate and less indicative of severity than symptoms. The aim here is not to exclude studies on technicalities, but to

exclude studies that clearly have major issues that may significantly change the outcome. We welcome feedback on improvements or corrections to this. The studies excluded are as follows, and the resulting forest plot is shown in Figure 11.

[Ader], very late stage, >50% on oxygen/ventilation at baseline.

[Alamdari], substantial unadjusted confounding by indication likely.

[Albanghali], unadjusted results with no group details, substantial unadjusted confounding by indication likely.

[Albani], substantial unadjusted confounding by indication likely, substantial confounding by time likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically.

[Alghamdi], unadjusted results with no group details, very late stage, ICU patients.

[Alghamdi (B)], confounding by indication is likely and adjustments do not consider COVID-19 severity at baseline.

[Alhamlan], substantial unadjusted confounding by indication likely, substantial confounding by time likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically.

[Alwafi], excessive unadjusted differences between groups.

[Annie], confounding by indication is likely and adjustments do not consider COVID-19 severity at baseline.

[Aparisi], unadjusted results with no group details.

[Awad], substantial confounding by time likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically, substantial unadjusted confounding by indication likely.

[Azaña Gómez], unadjusted results with no group details.

[Barbosa], excessive unadjusted differences between groups.

[Barra], unadjusted results with no group details.

[Bielza], unadjusted results with no group details.

[Boari], unadjusted results with no group details.

[Bosaeed], very late stage, >50% on oxygen/ventilation at baseline.

[Budhiraja], excessive unadjusted differences between groups.

[Cassione], not fully adjusting for the different baseline risk of systemic autoimmune patients.

[Chari], unadjusted results with no group details.

[Chechter], unadjusted results with no group details.

[Choi], excessive unadjusted differences between groups.

[Coll], unadjusted results with no group details.

[Cortez], unadjusted results with no group details.

[Cravedi], substantial unadjusted confounding by indication likely.

[de la Iglesia], not fully adjusting for the different baseline risk of systemic autoimmune patients.

[De Luna], unadjusted results with no group details, substantial unadjusted confounding by indication likely.

[Erden], unadjusted results with no group details.

[Fitzgerald], not fully adjusting for the baseline risk differences within systemic autoimmune patients.

[Fried], excessive unadjusted differences between groups, substantial unadjusted confounding by indication likely.

[Fung], not fully adjusting for the different baseline risk of systemic autoimmune patients.

[Gadhiya], substantial confounding by time likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically, substantial unadjusted confounding by indication likely.

[Gautret], excessive unadjusted differences between groups, results only for PCR status which may be significantly different to symptoms.

[Geleris], significant issues found with adjustments.

[Gendebien], not fully adjusting for the baseline risk differences within systemic autoimmune patients.

[Gendelman], not fully adjusting for the different baseline risk of systemic autoimmune patients.

[Gianfrancesco], not fully adjusting for the baseline risk differences within systemic autoimmune patients.

[Goldman], unadjusted results with no group details.

[Gupta], very late stage, >50% on oxygen/ventilation at baseline.

[Hall], unadjusted results with no group details.

[Hraiech], very late stage, ICU patients.

[Huang], significant unadjusted confounding possible.

[Huh], not fully adjusting for the different baseline risk of systemic autoimmune patients.

[Izoulet], excessive unadjusted differences between groups.

[Jacobs], unadjusted results with no group details, substantial confounding by time likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically.

[Juneja], excessive unadjusted differences between groups.

[Kamran], excessive unadjusted differences between groups.

[Kamstrup], not fully adjusting for the different baseline risk of systemic autoimmune patients.

[Karruli], unadjusted results with no group details.

[Kelly], substantial unadjusted confounding by indication likely.

[Konig], not fully adjusting for the baseline risk differences within systemic autoimmune patients.

[Krishnan], unadjusted results with no group details.

[Kuderer], substantial unadjusted confounding by indication likely.

[Küçükakkaş], minimal details of groups provided.

[Lamback], substantial confounding by time likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically.

[Laplana], not fully adjusting for the different baseline risk of systemic autoimmune patients.

[Lecronier], very late stage, >50% on oxygen/ventilation at baseline.

[Lotfy], substantial confounding by time likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically, substantial unadjusted confounding by indication likely.

[Luo], substantial unadjusted confounding by indication likely.

[Macias], not fully adjusting for the baseline risk differences within systemic autoimmune patients.

[Mahale], unadjusted results with no group details.

[Mahto], unadjusted results with no group details.

[Maldonado], treatment or control group size extremely small.

[Martin-Vicente], unadjusted results with no group details, treatment or control group size extremely small.

[McGrail], excessive unadjusted differences between groups.

[Menardi], excessive unadjusted differences between groups, substantial unadjusted confounding by indication likely.

[Mitchell], excessive unadjusted differences between groups.

[Mohandas], substantial unadjusted confounding by indication likely, unadjusted results with no group details, substantial confounding by time likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically.

[Mulhem], substantial unadjusted confounding by indication likely, substantial confounding by time likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically.

[Niwas], excessive unadjusted differences between groups.

[Oztas], not adjusting for the different baseline risk of systemic autoimmune patients, excessive unadjusted differences between groups.

[Pasquini], unadjusted results with no group details.

[Peters], excessive unadjusted differences between groups.

[Psevdos], unadjusted results with no group details, no treatment details, substantial confounding by time likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically, substantial unadjusted confounding by indication likely.

[Qin], unadjusted results with no group details.

[Ramírez-García], excessive unadjusted differences between groups, substantial unadjusted confounding by indication likely.

[Rangel], not fully adjusting for the different baseline risk of systemic autoimmune patients.

[Rao], unadjusted results with minimal group details.

[RECOVERY], excessive dosage in late stage patients, results do not apply to typical dosages.

[Rentsch], not fully adjusting for the baseline risk differences within systemic autoimmune patients, medication adherence unknown and may significantly change results.

[Rodriguez], unadjusted results with no group details.

[Rodriguez-Nava], substantial unadjusted confounding by indication likely, excessive unadjusted differences between groups, unadjusted results with no group details.

[Roger], substantial confounding by time likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically.

[Roig], unadjusted results with no group details.

[Roomi], substantial unadjusted confounding by indication likely.

[Rosenthal], confounding by indication is likely and adjustments do not consider COVID-19 severity at baseline.

[Roy], no serious outcomes reported and fast recovery in treatment and control groups, there is little room for a treatment to improve results.

[Saib], substantial unadjusted confounding by indication likely.

[Salazar], substantial unadjusted confounding by indication likely, unadjusted results with no group details.

[Saleemi], substantial unadjusted confounding by indication likely.

[Salehi], unadjusted results with no group details.

[Salvarani], not fully adjusting for the different baseline risk of systemic autoimmune patients.

[Samajdar], minimal details provided, unadjusted results with no group details, results may be significantly affected by survey bias.

[Sammartino], substantial confounding by time likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically.

[Sands], includes PCR+ patients that may be asymptomatic for COVID-19 but in hospital for other reasons, substantial unadjusted confounding by indication likely.

[Sarfaraz], substantial unadjusted confounding by indication likely, significant unadjusted confounding possible, unadjusted results with no group details.

[Sarhan], very late stage, >50% on oxygen/ventilation at baseline, significant unadjusted differences between groups.

[Satti], unadjusted results with no group details.

[Sbidian], significant issues found with adjustments.

[Schmidt], confounding by indication is likely and adjustments do not consider COVID-19 severity at baseline.

[Shoaibi], unadjusted results with no group details.

[Singer], not fully adjusting for the baseline risk differences within systemic autoimmune patients.

[Singh], confounding by indication is likely and adjustments do not consider COVID-19 severity at baseline.

[Smith], immortal time bias may significantly affect results.

[Solh], very late stage, >50% on oxygen/ventilation at baseline, substantial unadjusted confounding by indication likely.

[SOLIDARITY], excessive dosage in late stage patients, results do not apply to typical dosages, very late stage, >50% on oxygen/ventilation at baseline.

[Sosa-García], very late stage, >50% on oxygen/ventilation at baseline, substantial unadjusted confounding by indication likely.

[Soto], unadjusted results with no group details, substantial unadjusted confounding by indication likely, substantial confounding by time possible due to significant changes in SOC and treatment propensity near the start of the pandemic.

[Soto-Becerra], substantial unadjusted confounding by indication likely, includes PCR+ patients that may be asymptomatic for COVID-19 but in hospital for other reasons.

[Stewart], substantial unadjusted confounding by indication likely, substantial confounding by time likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically, includes PCR+ patients that may be asymptomatic for COVID-19 but in hospital for other reasons.

[Stewart (B)], substantial unadjusted confounding by indication likely, substantial confounding by time likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically, includes PCR+ patients that may be asymptomatic for COVID-19 but in hospital for other reasons.

[Stewart (C)], substantial unadjusted confounding by indication likely, substantial confounding by time likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically, includes PCR+ patients that may be asymptomatic for COVID-19 but in hospital for other reasons.

[Stewart (D)], substantial unadjusted confounding by indication likely, substantial confounding by time likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically, includes PCR+ patients that may be asymptomatic for COVID-19 but in hospital for other reasons.

[Stewart (E)], substantial unadjusted confounding by indication likely, substantial confounding by time likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically, includes PCR+ patients that may be asymptomatic for COVID-19 but in hospital for other reasons.

[Stewart (F)], substantial unadjusted confounding by indication likely, substantial confounding by time likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically, includes PCR+ patients that may be asymptomatic for COVID-19 but in hospital for other reasons.

[Stewart (G)], substantial unadjusted confounding by indication likely, substantial confounding by time likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically, includes PCR+ patients that may be asymptomatic for COVID-19 but in hospital for other reasons.

[Tamura], substantial unadjusted confounding by indication likely, substantial confounding by time likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically.

[Tehrani], substantial unadjusted confounding by indication likely, unadjusted results with no group details.

[Texeira], unadjusted results with no group details, no treatment details, substantial confounding by time likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically, substantial unadjusted confounding by indication likely.

[Trefond], not fully adjusting for the different baseline risk of systemic autoimmune patients, significant unadjusted confounding possible, excessive unadjusted differences between groups.

[Tu], unadjusted results with no group details.

[Ubaldo], substantial unadjusted confounding by indication likely, very late stage, ICU patients, unadjusted results with no group details.

[Ulrich], very late stage, >50% on oxygen/ventilation at baseline.

[Vernaz], substantial confounding by time likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically, substantial unadjusted confounding by indication likely.

[Vivanco-Hidalgo], not fully adjusting for the different baseline risk of systemic autoimmune patients.

[Wang (C)], confounding by indication is likely and adjustments do not consider COVID-19 severity at baseline.

[Xia], minimal details provided.

[Yegerov], unadjusted results with no group details.

[Çivriz Bozdağ], substantial confounding by time likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically.

[Çiyiltepe], treatment group only includes patients where treatment failed resulting in ICU admission.

223 hydroxychloroquine COVID-19 studies after exclusions

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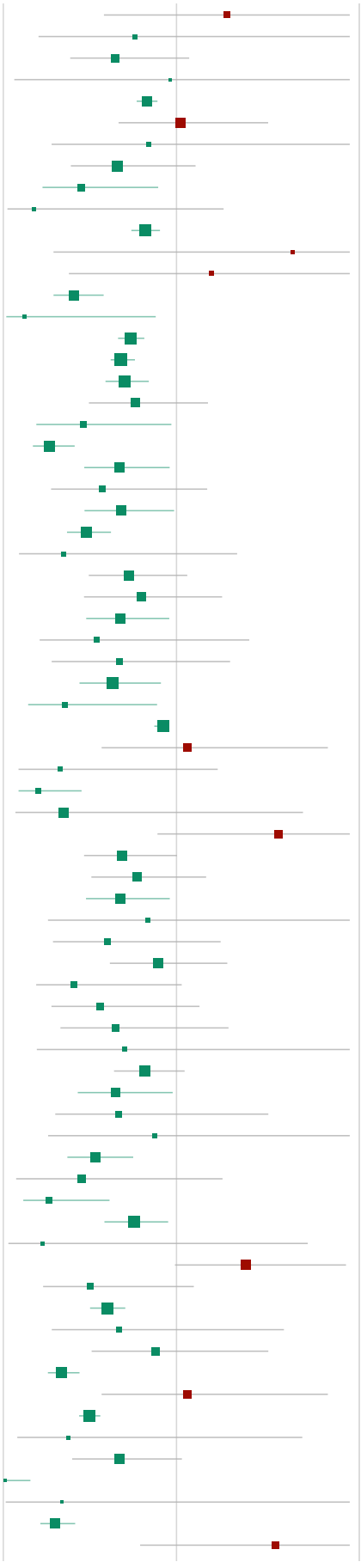
	Improvement	RR [CI]		Treatment	Control
Huang (RCT)	92%	0.08 [0.01-1.32]	no recov.	0/10	6/12
Esper	64%	0.36 [0.15-0.87]	hosp.	8/412	12/224
Ashraf	68%	0.32 [0.10-1.10]	death	10/77	2/5
Huang (ES)	59%	0.41 [0.26-0.64]	viral time	32 (n)	37 (n)
Guérin	61%	0.39 [0.02-9.06]	death	0/20	1/34
Chen (RCT)	72%	0.28 [0.11-0.74]	viral time	18 (n)	12 (n)
Derwand	79%	0.21 [0.03-1.47]	death	1/141	13/377
Mitjà (RCT)	16%	0.84 [0.35-2.03]	hosp.	8/136	11/157
Skipper (RCT)	37%	0.63 [0.21-1.91]	death/hosp.	5/231	8/234
Hong	65%	0.35 [0.13-0.72]	viral+	42 (n)	48 (n)
Bernabeu-Wittel	59%	0.41 [0.36-0.95]	death	189 (n)	83 (n)
Yu (ES)	85%	0.15 [0.02-1.05]	death	1/73	238/2,604
Ly	56%	0.44 [0.26-0.75]	death	18/116	29/110
Ip	55%	0.45 [0.11-1.85]	death	2/97	44/970
Heras	96%	0.04 [0.02-0.09]	death	8/70	16/30
Kirenga	26%	0.74 [0.47-1.17]	recov. time	29 (n)	27 (n)
Sulaiman	64%	0.36 [0.17-0.80]	death	7/1,817	54/3,724
Guisado-Vasco (ES)	67%	0.33 [0.05-1.55]	death	2/65	139/542
Szente Fonseca	64%	0.36 [0.20-0.67]	hosp.	25/175	89/542
Cadegiani	81%	0.19 [0.01-3.88]	death	0/159	2/137
Simova	94%	0.06 [0.00-1.13]	hosp.	0/33	2/5
Omrani (RCT)	12%	0.88 [0.26-2.94]	hosp.	7/304	4/152
Agusti	68%	0.32 [0.06-1.67]	progression	2/87	4/55
Su	85%	0.15 [0.04-0.57]	progression	n/a	n/a
Amaravadi (RCT)	60%	0.40 [0.13-1.28]	no recov.	3/15	6/12
Mokhtari	70%	0.30 [0.20-0.45]	death	27/7,295	287/21,464
Corradini (ES)	67%	0.33 [0.14-0.78]	death	641 (n)	102 (n)
Million	83%	0.17 [0.06-0.48]	death	5/8,315	11/2,114
Sobngwi (RCT)	52%	0.48 [0.09-2.58]	no recov.	2/95	4/92
Rodrigues (RCT)	-200%	3.00 [0.13-71.6]	hosp.	1/42	0/42
Sawanpanyalert	42%	0.58 [0.18-1.91]	progression	n/a	n/a
Atipornwan.. (RCT)	-150%	2.50 [0.10-59.6]	progression	1/60	0/30
Rouamba (ES)	73%	0.27 [0.09-1.02]	progression	23/399	4/33
Avezum (RCT)	1%	0.99 [0.29-3.41]	death	5/687	5/682
Roy-García (RCT)	-100%	2.00 [0.19-20.9]	progression	2/31	1/31
Early treatment	64%	0.36 [0.29-0.46]		173/21,913	992/34,723

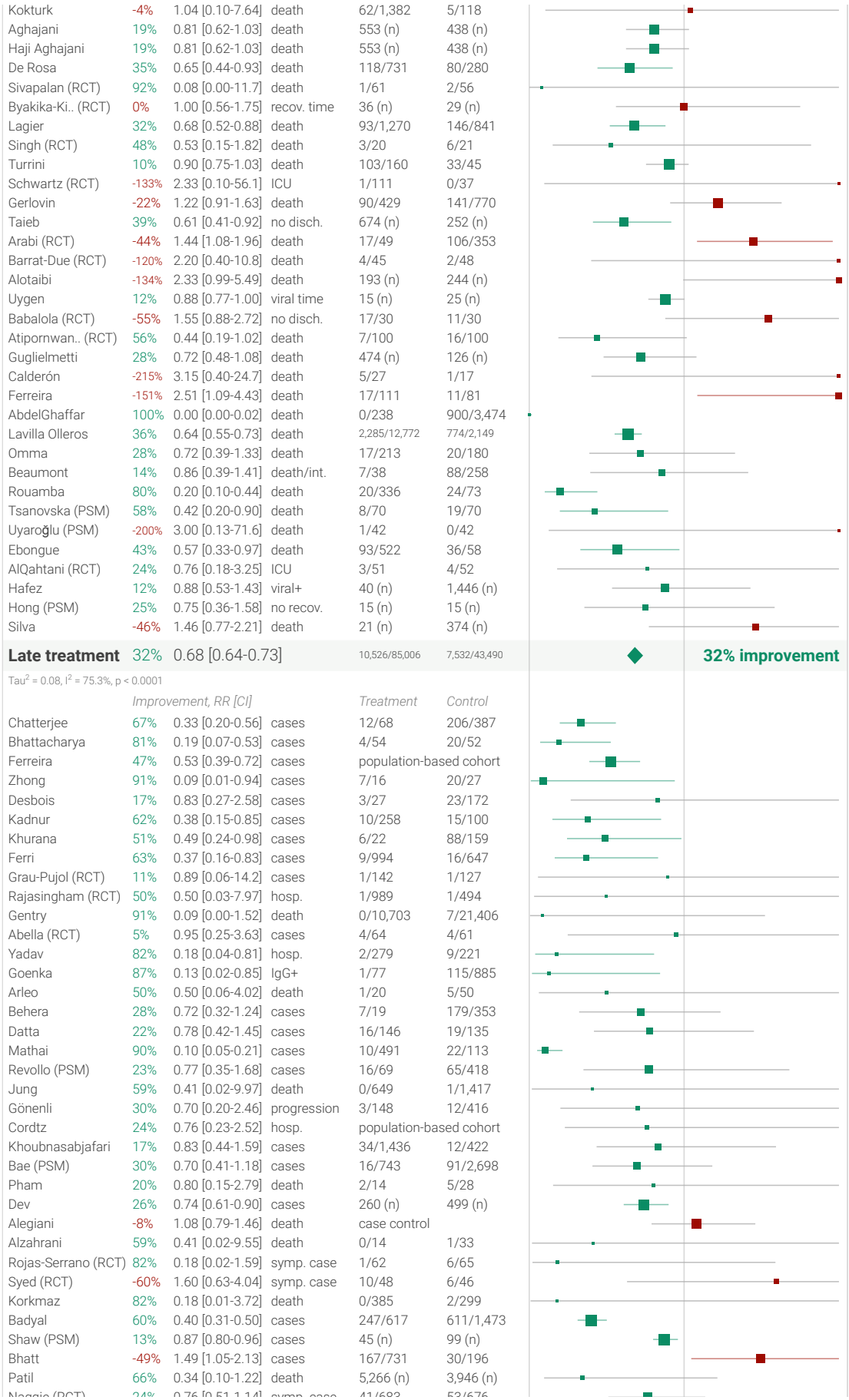
64% improvement

$Tau^2 = 0.19$, $I^2 = 48.8\%$, $p < 0.0001$

	Improvement	RR [CI]		Treatment	Control
Chen (RCT)	29%	0.71 [0.29-1.74]	progression	5/15	7/15
Zhong	80%	0.20 [0.08-0.52]	viral+	5/115	17/82
Chen (RCT)	57%	0.43 [0.19-0.97]	pneumonia	6/31	14/31
Tang (RCT)	21%	0.79 [0.38-1.62]	viral+	11/75	14/75
Magagnoli	11%	0.89 [0.45-1.77]	death	39/148	18/163
Auld	-3%	1.03 [0.67-1.57]	death	33/114	29/103
Sánchez-Álvarez	46%	0.54 [0.34-0.84]	death	322 (n)	53 (n)
Mallat	-203%	3.03 [1.11-7.69]	viral time	23 (n)	11 (n)
Membrillo de No..	55%	0.45 [0.29-0.71]	death	27/123	21/43
Alberici	43%	0.57 [0.24-1.13]	death	17/72	9/22
Rosenberg	-35%	1.35 [0.76-2.40]	death	189/735	28/221
Shabrawishi	15%	0.85 [0.45-1.62]	viral+	12/45	15/48
Mahévas	-20%	1.20 [0.40-3.30]	death	9/84	8/89
Yu	60%	0.40 [0.22-0.72]	death	9/48	238/502
Kim	51%	0.49 [0.28-0.87]	hosp. time	22 (n)	40 (n)
Luo	32%	0.68 [0.08-5.88]	death	19 (n)	264 (n)
Ip	1%	0.99 [0.80-1.22]	death	432/1,914	115/598
Huang	67%	0.33 [0.19-0.57]	viral time	197 (n)	176 (n)
Rogado	92%	0.08 [0.00-0.87]	death	1/8	7/9
Paccoud	11%	0.89 [0.23-3.47]	death	21/38	26/46
Faíco-Filho	81%	0.19 [0.00-8.66]	viral rate	34 (n)	32 (n)
Fontana	50%	0.50 [0.16-1.55]	death	4/12	2/3
Bousquet	43%	0.57 [0.24-1.36]	death	5/27	23/81
Lagier	59%	0.41 [0.27-0.62]	death	35/3,119	58/618
Komissarov	-25%	1.25 [0.71-2.21]	viral load	26 (n)	10 (n)
Mikami	47%	0.53 [0.41-0.68]	death	575/2,077	231/743
Martinez-Lopez	33%	0.67 [0.39-1.14]	death	47/148	9/19
Arshad	51%	0.49 [0.39-0.60]	death	162/1,202	108/409
An	3%	0.97 [0.57-1.67]	viral+	31 (n)	195 (n)
Rivera-Izquierdo	19%	0.81 [0.24-2.76]	death	215 (n)	23 (n)

Chen	-29%	1.29 [0.58-2.86]	viral+	16/28	4/9
Chen (RCT)	24%	0.76 [0.20-2.84]	viral+	4/21	3/12
Trullàs	36%	0.64 [0.39-1.07]	death	20/66	16/34
Lyngbakken (RCT)	4%	0.96 [0.06-14.6]	death	1/27	1/26
Bernaola	17%	0.83 [0.77-0.89]	death	236/1,498	28/147
Rivera	-2%	1.02 [0.67-1.53]	death	44/179	59/327
Cavalcanti (RCT)	16%	0.84 [0.28-2.53]	death	8/331	5/173
D'Arminio Monfo..	34%	0.66 [0.39-1.11]	death	53/197	47/92
Davido	55%	0.45 [0.23-0.89]	int./hosp.	12/80	13/40
Yu	83%	0.17 [0.02-1.27]	progression	1/231	32/1,291
Berenguer	18%	0.82 [0.74-0.90]	death	681/2,618	438/1,377
Kalligeros	-67%	1.67 [0.29-9.36]	death	36 (n)	72 (n)
Abd-Elsalam (RCT)	-20%	1.20 [0.38-3.80]	death	6/97	5/97
Pinato	59%	0.41 [0.29-0.58]	death	30/182	181/446
Dubernet	88%	0.12 [0.02-0.88]	ICU	1/17	9/19
Gonzalez	27%	0.73 [0.66-0.81]	death	1,246/8,476	341/1,168
Catteau	32%	0.68 [0.62-0.76]	death	804/4,542	957/3,533
Di Castelnuovo	30%	0.70 [0.59-0.84]	death	386/2,634	90/817
Synolaki	24%	0.76 [0.49-1.18]	death	21/98	60/214
Heberto	54%	0.46 [0.19-0.97]	death	139 (n)	115 (n)
Lauriola	74%	0.27 [0.17-0.41]	death	102/297	35/63
Ashinyo	33%	0.67 [0.47-0.96]	hosp. time	61 (n)	61 (n)
Serrano	43%	0.57 [0.28-1.18]	death	6/14	6/8
Lammers	32%	0.68 [0.47-0.99]	death/ICU	30/189	101/498
Ayerbe	52%	0.48 [0.37-0.62]	death	237/1,857	49/162
Almazrou	65%	0.35 [0.09-1.35]	ventilation	3/95	6/66
Nachega	28%	0.72 [0.49-1.06]	death	69/630	28/96
Guisado-Vasco	20%	0.80 [0.47-1.26]	death	127/558	14/49
Ñamendys-S.. (ICU)	32%	0.68 [0.48-0.96]	death	24/54	42/64
Dubee (RCT)	46%	0.54 [0.21-1.42]	death	6/124	11/123
Lano	33%	0.67 [0.28-1.31]	death	56 (n)	66 (n)
Frontera (PSM)	37%	0.63 [0.44-0.91]	death	121/1,006	424/2,467
López	64%	0.36 [0.14-0.89]	progression	5/36	14/36
Núñez-Gil	8%	0.92 [0.87-0.94]	death	200/686	100/268
Self (RCT)	-6%	1.06 [0.57-1.87]	death	25/241	25/236
Águila-Gordo	67%	0.33 [0.09-1.24]	death	151/346	47/70
Sheshah	80%	0.20 [0.09-0.45]	death	267 (n)	33 (n)
Falcone (PSM)	65%	0.35 [0.07-1.73]	death	40/238	30/77
Burdick	-59%	1.59 [0.89-2.83]	death	142 (n)	148 (n)
van Halem	32%	0.68 [0.47-1.00]	death	34/164	47/155
Rodriguez-Gonzalez	23%	0.77 [0.51-1.17]	death	251/1,148	17/60
Lambermont	32%	0.68 [0.48-0.96]	death	97/225	14/22
Abdulrahman (PSM)	17%	0.83 [0.26-2.69]	death	5/223	6/223
Capsoni	40%	0.60 [0.29-1.25]	ventilation	12/40	6/12
Peng	11%	0.89 [0.62-1.29]	progression	29/453	256/3,567
Modrák	59%	0.41 [0.19-1.03]	death	108 (n)	105 (n)
Ozturk	44%	0.56 [0.28-1.13]	death	165/1,127	6/23
Guglielmetti	35%	0.65 [0.33-1.30]	death	181 (n)	37 (n)
Johnston (RCT)	30%	0.70 [0.19-2.54]	hosp.	5/148	4/83
Alqassieh	18%	0.82 [0.64-1.05]	hosp. time	63 (n)	68 (n)
Tan	35%	0.65 [0.43-0.98]	hosp. time	8 (n)	277 (n)
Naseem	33%	0.67 [0.30-1.53]	death	77 (n)	1,137 (n)
Orioli	13%	0.87 [0.26-2.94]	death	8/55	3/18
Signes-Costa	47%	0.53 [0.37-0.75]	death	4,854 (n)	993 (n)
Matangila	55%	0.45 [0.07-1.27]	death	25/147	8/13
Cangiano	73%	0.27 [0.12-0.61]	death	5/33	37/65
Taccone (ICU)	25%	0.75 [0.58-0.95]	death	449/1,308	183/439
Güner	77%	0.23 [0.03-1.76]	ICU	604 (n)	100 (n)
Li	-40%	1.40 [0.99-1.98]	viral time	18 (n)	19 (n)
Li	50%	0.50 [0.23-1.10]	no disch.	14 (n)	14 (n)
Di Castelnuovo	40%	0.60 [0.50-0.70]	death	3,270 (n)	1,000 (n)
Ouedraogo	33%	0.67 [0.28-1.62]	death	397 (n)	59 (n)
Hernandez-C.. (RCT)	12%	0.88 [0.51-1.53]	death	106 (n)	108 (n)
Purwati (RCT)	66%	0.34 [0.26-0.44]	viral+	38/121	111/119
Thompson (RCT)	-6%	1.06 [0.57-1.87]	death	25/241	25/236
Lora-Tamayo	50%	0.50 [0.44-0.56]	death	7,192 (n)	1,361 (n)
Beltran Gon.. (RCT)	63%	0.37 [0.08-1.73]	death	2/33	6/37
Salvador	33%	0.67 [0.40-1.03]	death	28/121	58/124
Barry	99%	0.01 [0.00-0.16]	death	0/6	91/599
Reis (RCT)	66%	0.34 [0.01-8.30]	death	0/214	1/227
Corradini	70%	0.30 [0.21-0.41]	death	1,439 (n)	274 (n)
Réa-Neto (RCT)	-57%	1.57 [0.79-3.13]	death	16/53	10/52





Kokturk	-4%	1.04 [0.10-7.64]	death	62/1,382	5/118
Aghajani	19%	0.81 [0.62-1.03]	death	553 (n)	438 (n)
Haji Aghajani	19%	0.81 [0.62-1.03]	death	553 (n)	438 (n)
De Rosa	35%	0.65 [0.44-0.93]	death	118/731	80/280
Sivapalan (RCT)	92%	0.08 [0.00-11.7]	death	1/61	2/56
Byakika-Ki.. (RCT)	0%	1.00 [0.56-1.75]	recov. time	36 (n)	29 (n)
Lagier	32%	0.68 [0.52-0.88]	death	93/1,270	146/841
Singh (RCT)	48%	0.53 [0.15-1.82]	death	3/20	6/21
Turrini	10%	0.90 [0.75-1.03]	death	103/160	33/45
Schwartz (RCT)	-133%	2.33 [0.10-56.1]	ICU	1/111	0/37
Gerlovin	-22%	1.22 [0.91-1.63]	death	90/429	141/770
Taieb	39%	0.61 [0.41-0.92]	no disch.	674 (n)	252 (n)
Arabi (RCT)	-44%	1.44 [1.08-1.96]	death	17/49	106/353
Barrat-Due (RCT)	-120%	2.20 [0.40-10.8]	death	4/45	2/48
Alotaibi	-134%	2.33 [0.99-5.49]	death	193 (n)	244 (n)
Uygen	12%	0.88 [0.77-1.00]	viral time	15 (n)	25 (n)
Babalola (RCT)	-55%	1.55 [0.88-2.72]	no disch.	17/30	11/30
Atipornwan.. (RCT)	56%	0.44 [0.19-1.02]	death	7/100	16/100
Guglielmetti	28%	0.72 [0.48-1.08]	death	474 (n)	126 (n)
Calderón	-215%	3.15 [0.40-24.7]	death	5/27	1/17
Ferreira	-151%	2.51 [1.09-4.43]	death	17/111	11/81
AbdelGhaffar	100%	0.00 [0.00-0.02]	death	0/238	900/3,474
Lavilla Olleros	36%	0.64 [0.55-0.73]	death	2,285/12,772	774/2,149
Omma	28%	0.72 [0.39-1.33]	death	17/213	20/180
Beaumont	14%	0.86 [0.39-1.41]	death/int.	7/38	88/258
Rouamba	80%	0.20 [0.10-0.44]	death	20/336	24/73
Tsanovska (PSM)	58%	0.42 [0.20-0.90]	death	8/70	19/70
Uyaroğlu (PSM)	-200%	3.00 [0.13-71.6]	death	1/42	0/42
Ebongue	43%	0.57 [0.33-0.97]	death	93/522	36/58
AlQahtani (RCT)	24%	0.76 [0.18-3.25]	ICU	3/51	4/52
Hafez	12%	0.88 [0.53-1.43]	viral+	40 (n)	1,446 (n)
Hong (PSM)	25%	0.75 [0.36-1.58]	no recov.	15 (n)	15 (n)
Silva	-46%	1.46 [0.77-2.21]	death	21 (n)	374 (n)
Late treatment	32%	0.68 [0.64-0.73]		10,526/85,006	7,532/43,490

32% improvement

$Tau^2 = 0.08$, $I^2 = 75.3\%$, $p < 0.0001$

	Improvement, RR [CI]			*Treatment*	*Control*
Chatterjee	67%	0.33 [0.20-0.56]	cases	12/68	206/387
Bhattacharya	81%	0.19 [0.07-0.53]	cases	4/54	20/52
Ferreira	47%	0.53 [0.39-0.72]	cases	population-based cohort	
Zhong	91%	0.09 [0.01-0.94]	cases	7/16	20/27
Desbois	17%	0.83 [0.27-2.58]	cases	3/27	23/172
Kadnur	62%	0.38 [0.15-0.85]	cases	10/258	15/100
Khurana	51%	0.49 [0.24-0.98]	cases	6/22	88/159
Ferri	63%	0.37 [0.16-0.83]	cases	9/994	16/647
Grau-Pujol (RCT)	11%	0.89 [0.06-14.2]	cases	1/142	1/127
Rajasingham (RCT)	50%	0.50 [0.03-7.97]	hosp.	1/989	1/494
Gentry	91%	0.09 [0.00-1.52]	death	0/10,703	7/21,406
Abella (RCT)	5%	0.95 [0.25-3.63]	cases	4/64	4/61
Yadav	82%	0.18 [0.04-0.81]	hosp.	2/279	9/221
Goenka	87%	0.13 [0.02-0.85]	IgG+	1/77	115/885
Arleo	50%	0.50 [0.06-4.02]	death	1/20	5/50
Behera	28%	0.72 [0.32-1.24]	cases	7/19	179/353
Datta	22%	0.78 [0.42-1.45]	cases	16/146	19/135
Mathai	90%	0.10 [0.05-0.21]	cases	10/491	22/113
Revollo (PSM)	23%	0.77 [0.35-1.68]	cases	16/69	65/418
Jung	59%	0.41 [0.02-9.97]	death	0/649	1/1,417
Gönenli	30%	0.70 [0.20-2.46]	progression	3/148	12/416
Cordtz	24%	0.76 [0.23-2.52]	hosp.	population-based cohort	
Khoubnasabjafari	17%	0.83 [0.44-1.59]	cases	34/1,436	12/422
Bae (PSM)	30%	0.70 [0.41-1.18]	cases	16/743	91/2,698
Pham	20%	0.80 [0.15-2.79]	death	2/14	5/28
Dev	26%	0.74 [0.61-0.90]	cases	260 (n)	499 (n)
Alegiani	-8%	1.08 [0.79-1.46]	death	case control	
Alzahrani	59%	0.41 [0.02-9.55]	death	0/14	1/33
Rojas-Serrano (RCT)	82%	0.18 [0.02-1.59]	symp. case	1/62	6/65
Syed (RCT)	-60%	1.60 [0.63-4.04]	symp. case	10/48	6/46
Korkmaz	82%	0.18 [0.01-3.72]	death	0/385	2/299
Badyal	60%	0.40 [0.31-0.50]	cases	247/617	611/1,473
Shaw (PSM)	13%	0.87 [0.80-0.96]	cases	45 (n)	99 (n)
Bhatt	-49%	1.49 [1.05-2.13]	cases	167/731	30/196
Patil	66%	0.34 [0.10-1.22]	death	5,266 (n)	3,946 (n)
Naggie (RCT)	24%	0.76 [0.51-1.14]	symp. case	41/683	53/676

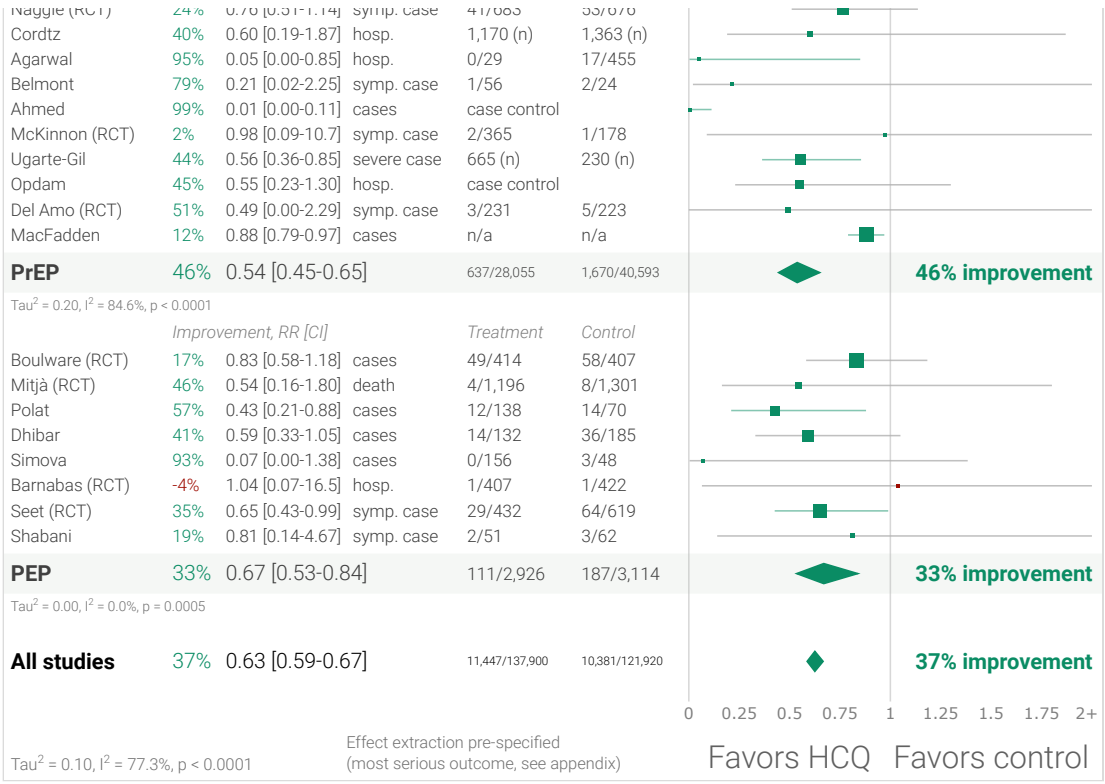


Figure 11. *Random effects meta-analysis excluding studies with significant issues. Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details. (ES) indicates the early treatment subset of a study (these are not included in the overall results).*

Heterogeneity

Heterogeneity in COVID-19 studies arises from many factors including:

Treatment delay. The time between infection or the onset of symptoms and treatment may critically affect how well a treatment works. For example an antiviral may be very effective when used early but may not be effective in late stage disease, and may even be harmful. Oseltamivir, for example, is generally only considered effective for influenza when used within 0-36 or 0-48 hours ***[McLean, Treanor]***. Figure 12 shows a mixed-effects meta-regression of efficacy as a function of treatment delay in HCQ COVID-19 studies, showing that efficacy declines rapidly with treatment delay. Early treatment is critical for COVID-19.

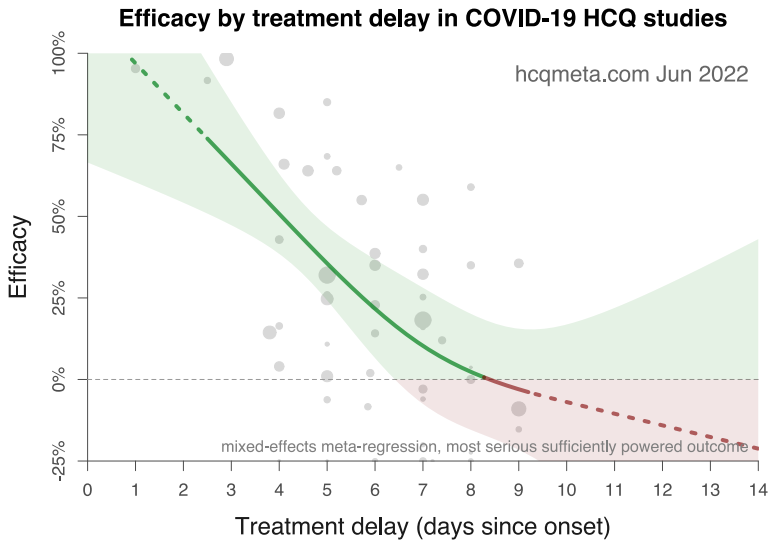


Figure 12. *Meta-regression showing efficacy as a function of treatment delay in COVID-19 HCQ studies. Early treatment is critical.*

Patient demographics. Details of the patient population including age and comorbidities may critically affect how well a treatment works. For example, many COVID-19 studies with relatively young low-comorbidity patients show all patients recovering quickly with or without treatment. In such cases, there is little room for an effective treatment to improve results (as in ***[López-Medina]***).

Effect measured. Efficacy may differ significantly depending on the effect measured, for example a treatment may be very effective at reducing mortality, but less effective at minimizing cases or hospitalization. Or a treatment may have no effect on viral clearance while still being effective at reducing mortality.

Variants. There are many different variants of SARS-CoV-2 and efficacy may depend critically on the distribution of variants encountered by the patients in a study. For example, the Gamma variant shows significantly different characteristics ***[Faria, Karita, Nonaka, Zavascki]***. Different mechanisms of action may be more or less effective depending on variants, for example the viral entry process for the omicron variant has moved towards TMPRSS2-independent fusion, suggesting that TMPRSS2 inhibitors may be less effective ***[Peacock, Willett]***.

Regimen. Effectiveness may depend strongly on the dosage and treatment regimen.

Treatments. The use of other treatments may significantly affect outcomes, including anything from supplements, other medications, or other kinds of treatment such as prone positioning.

The distribution of studies will alter the outcome of a meta analysis. Consider a simplified example where everything is equal except for the treatment delay, and effectiveness decreases to zero or below with increasing delay. If there are many studies using very late treatment, the outcome may be negative, even though the treatment may be very effective when used earlier.

In general, by combining heterogeneous studies, as all meta analyses do, we run the risk of obscuring an effect by including studies where the treatment is less effective, not effective, or harmful.

When including studies where a treatment is less effective we expect the estimated effect size to be lower than that for the optimal case. We do not *a priori* expect that pooling all studies will create a positive result for an effective treatment. Looking at all studies is valuable for providing an overview of all research, important to avoid cherry-picking, and informative when a positive result is found despite combining less-optimal situations. However, the resulting estimate does not apply to specific cases such as early treatment in high-risk populations.

HCQ studies vary widely in all the factors above. We find a significant effect based on treatment delay. Early treatment shows consistently positive results, while late treatment results are very mixed. Closer analysis may identify factors related to efficacy among this group, for example treatment may be more effective in certain popuations, or more fine-grained analysis of treatment delay may identify a point after which treatment is ineffective.

Discussion

Publication bias. Publishing is often biased towards positive results, which we would need to adjust for when analyzing the percentage of positive results. Studies that require less effort are considered to be more susceptible to publication bias. Prospective trials that involve significant effort are likely to be published regardless of the result, while retrospective studies are more likely to exhibit bias. For example, researchers may perform preliminary analysis with minimal effort and the results may influence their decision to continue. Retrospective studies also provide more opportunities for the specifics of data extraction and adjustments to influence results.

For HCQ, 75.6% of prospective studies report positive effects, compared to 71.3% of retrospective studies, suggesting a bias toward publishing negative results. The median effect size for prospective studies is 27% improvement, compared to 22% for retrospective studies. Figure 13 shows a scatter plot of results for prospective and retrospective studies.

Figure 14 shows the results by region of the world, for all regions that have > 5 studies. Studies from North America are 2.6 times more likely to report negative results than studies from the rest of the world combined, 52.5% vs. 20.2%, two-tailed z test -5.62, p = 0.0000000191. ***[Berry]*** performed an independent analysis which also showed bias toward negative results for US-based research.

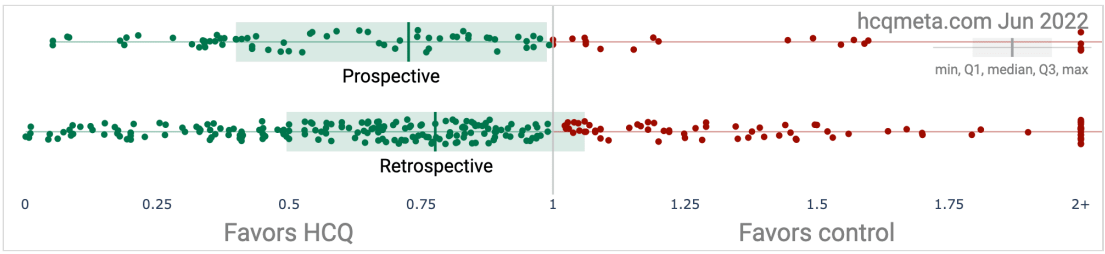


Figure 13. *Prospective vs. retrospective studies.*

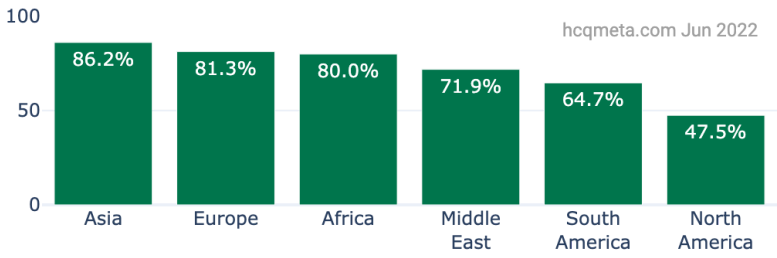


Figure 15. *Results by region.*

The lack of bias towards positive results is not very surprising. Both negative and positive results are very important given the current use of HCQ for COVID-19 around the world, evidence of which can be found in the studies analyzed here, government protocols, and news reports, for example *[AFP, AfricaFeeds, Africanews, Afrik.com, Al Arabia, Al-bab, Anadolu Agency, Anadolu Agency (B), Archyde, Barron's, Barron's (B), BBC, Belayneh, A., Bianet, CBS News, Challenge, Dr. Goldin, Efecto Cocuyo, Expats.cz, Face 2 Face Africa, Filipova, France 24, France 24 (B), Franceinfo, Global Times, Government of China, Government of India, Government of Venezuela, GulfInsider, Le Nouvel Afrik, LifeSiteNews, Medical World Nigeria, Medical Xpress, Medical Xpress (B), Middle East Eye, Ministerstva Zdravotnictví, Ministry of Health of Ukraine, Ministry of Health of Ukraine (B), Morocco World News, Mosaique Guinee, Nigeria News World, NPR News, Oneindia, Pan African Medical Journal, Parola, Pilot News, PledgeTimes, Pleno.News, Q Costa Rica, Rathi, Russian Government, Russian Government (B), Teller Report, The Africa Report, The Australian, The BL, The East African, The Guardian, The Indian Express, The Moscow Times, The North Africa Post, The Tico Times, Ukrinform, Vanguard, Voice of America]*.

We also note a bias towards publishing negative results by certain journals and press organizations, with scientists reporting difficulty publishing positive results *[Boulware, Meeus, Meneguesso]*. *[Meeus]*, for example, report that their paper with 4,000 patients reporting favourable outcomes for HCQ+AZ was rejected without peer review from the editors of four different journals.

Although 251 studies show positive results, The New York Times, for example, has only written articles for studies that claim HCQ is not effective *[The New York Times, The New York Times (B), The New York Times (C)]*. As of September 10, 2020, The New York Times still claims that there is clear evidence that HCQ is not effective for COVID-19 *[The New York Times (D)]*. As of October 9, 2020, the United States National Institutes of Health recommends against HCQ for both hospitalized and non-hospitalized patients *[United States National Institutes of Health]*.

Physician case series results. Table 3 shows the reported results of physicians that use early treatments for COVID-19, compared to the results for a non-treating physician (this physician reportedly prescribed early treatment for themself, but not for patients *[medicospelavidacovid19.com.br]*). The treatments used vary between physicians. Almost all report using ivermectin and/or HCQ, and most use additional treatments in combination. A more detailed analysis requires information on the patient populations, however results are consistent with the extensive controlled trial evidence that shows a significant reduction in risk with early treatments, and improved results with the use of multiple treatments.

LATE TREATMENT						
Physician / Team	*Location*	*Patients*	*Hospitalization*		*Mortality*	
Dr. David Uip (*)	Brazil	2,200	38.6% (850)	Ref.	2.5% (54)	Ref.
EARLY TREATMENT - 32 physicians/teams						
Physician / Team	*Location*	*Patients*	*Hospitalization*	*Improvement*	*Mortality*	*Improvement*
Dr. Roberto Alfonso Accinelli 0/360 deaths for treatment within 3 days	Peru	1,265			0.6% (7)	77.5%
Dr. Mohammed Tarek Alam patients up to 84 years old	Bangladesh	100			0.0% (0)	100.0%
Dr. Oluwagbenga Alonge	Nigeria	310			0.0% (0)	100.0%
Dr. Raja Bhattacharya up to 88yo, 81% comorbidities	India	148			1.4% (2)	44.9%
Dr. Flavio Cadegiani	Brazil	3,450	0.1% (4)	99.7%	0.0% (0)	100.0%
Dr. Alessandro Capucci	Italy	350	4.6% (16)	88.2%		
Dr. Shankara Chetty	South Africa	8,000			0.0% (0)	100.0%
Dr. Deborah Chisholm	USA	100			0.0% (0)	100.0%
Dr. Ryan Cole	USA	400	0.0% (0)	100.0%	0.0% (0)	100.0%
Dr. Marco Cosentino vs. 3-3.8% mortality during period; earlier treatment better	Italy	392	6.4% (25)	83.5%	0.3% (1)	89.6%
Dr. Jeff Davis	USA	6,000			0.0% (0)	100.0%
Dr. Dhanajay	India	500			0.0% (0)	100.0%
Dr. Bryan Tyson & Dr. George Fareed	USA	4,375	0.2% (9)	99.5%	0.1% (3)	97.2%
Dr. Heather Gessling	USA	1,500			0.1% (1)	97.3%
Dr. Ellen Guimarães	Brazil	500	1.6% (8)	95.9%	0.4% (2)	83.7%
Dr. Syed Haider	USA	4,000	0.1% (5)	99.7%	0.0% (0)	100.0%
Dr. Mark Hancock	USA	24			0.0% (0)	100.0%
Dr. Mollie James	USA	3,500	1.1% (40)	97.0%	0.0% (1)	98.8%
Dr. Roberta Lacerda	Brazil	550	1.5% (8)	96.2%	0.4% (2)	85.2%
Dr. Ben Marble	USA	150,000			0.0% (4)	99.9%
Dr. Edimilson Migowski	Brazil	2,000	0.3% (7)	99.1%	0.1% (2)	95.9%
Dr. Abdulrahman Mohana	Saudi Arabia	2,733			0.0% (0)	100.0%
Dr. Carlos Nigro	Brazil	5,000	0.9% (45)	97.7%	0.5% (23)	81.3%
Dr. Benoit Ochs	Luxembourg	800			0.0% (0)	100.0%
Dr. Valerio Pascua one death for a patient presenting on the 5th day in need of supplemental oxygen	Honduras	415	6.3% (26)	83.8%	0.2% (1)	90.2%
Dr. Brian Proctor	USA	869	2.3% (20)	94.0%	0.2% (2)	90.6%

Dr. Anastacio Queiroz	Brazil	700			0.0% (0)	100.0%
Dr. Didier Raoult	France	8,315	2.6% (214)	93.3%	0.1% (5)	97.6%
Dr. Karin Ried up to 99yo, 73% comorbidities, av. age 63	Turkey	237			0.4% (1)	82.8%
Dr. Roman Rozencwaig patients up to 86 years old	Canada	80			0.0% (0)	100.0%
Dr. Vipul Shah	India	8,000			0.1% (5)	97.5%
Dr. Vladimir Zelenko	USA	2,200	0.5% (12)	98.6%	0.1% (2)	96.3%
Mean improvement with early treatment protocols		219,013	Hospitalization	**95.1%**	Mortality	**93.7%**

Table 3. *Physician results with early treatment protocols compared to no early treatment.* [(*)] *Dr. Uip reportedly prescribed early treatment for himself, but not for patients* ***[medicospelavidacovid19.com.br]****.*

Funnel plot analysis. Funnel plots have traditionally been used for analyzing publication bias. This is invalid for COVID-19 acute treatment trials — the underlying assumptions are invalid, which we can demonstrate with a simple example. Consider a set of hypothetical perfect trials with no bias. Figure 16 plot A shows a funnel plot for a simulation of 80 perfect trials, with random group sizes, and each patient's outcome randomly sampled (10% control event probability, and a 30% effect size for treatment). Analysis shows no asymmetry ($p > 0.05$). In plot B, we add a single typical variation in COVID-19 treatment trials — treatment delay. Consider that efficacy varies from 90% for treatment within 24 hours, reducing to 10% when treatment is delayed 3 days. In plot B, each trial's treatment delay is randomly selected. Analysis now shows highly significant asymmetry, $p < 0.0001$, with six variants of Egger's test all showing $p < 0.05$ ***[Egger, Harbord, Macaskill, Moreno, Peters (B), Rothstein, Rücker, Stanley]***. Note that these tests fail even though treatment delay is uniformly distributed. In reality treatment delay is more complex — each trial has a different distribution of delays across patients, and the distribution across trials may be biased (e.g., late treatment trials may be more common). Similarly, many other variations in trials may produce asymmetry, including dose, administration, duration of treatment, differences in SOC, comorbidities, age, variants, and bias in design, implementation, analysis, and reporting.

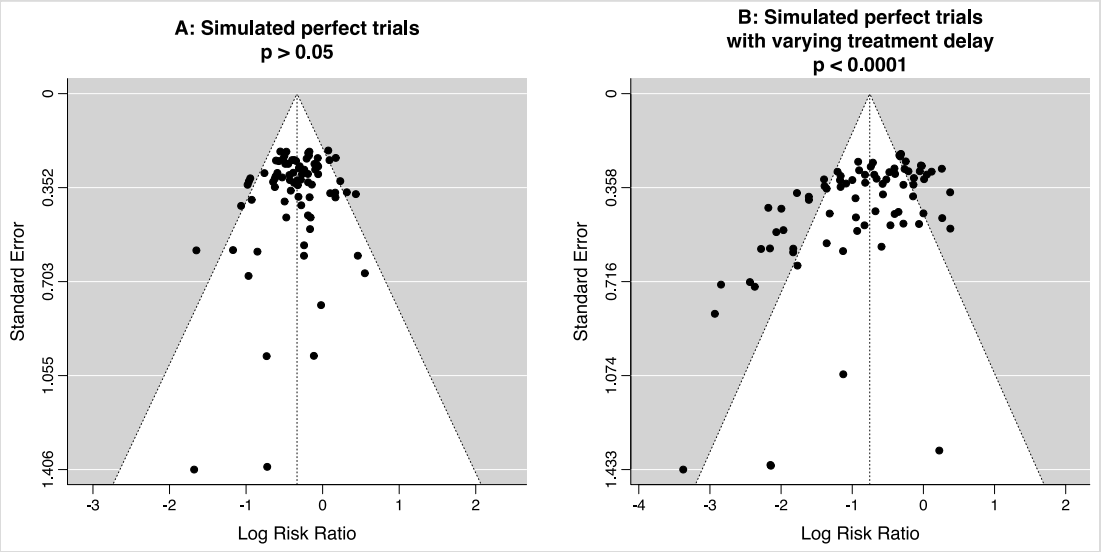


Figure 16. *Example funnel plot analysis for simulated perfect trials.*

Treatment details. We focus here on the question of whether HCQ is effective or not for COVID-19. Studies vary significantly in terms of treatment delay, treatment regimen, patients characteristics, and (for the pooled effects analysis) outcomes, as reflected in the high degree of heterogeneity. However, early treatment consistently shows benefits. 92% of early treatment studies report a positive effect, with an estimated reduction of 63% in the effect measured (death, hospitalization, etc.) in the random effects meta-analysis, RR 0.37 [0.30-0.47].

Negative Meta Analyses

Generally, it is easy to choose inclusion criteria and assign biased risk evaluations in order to produce any desired outcome in a meta analysis.

COVID-19 treatment studies have many sources of heterogeneity which affect the results, including treatment delay (time from infection or the onset of symptoms), patient population (age, comorbidities), the effect measured and details of the measurement, distribution of SARS-CoV-2 variants, dosage/regimen, and other treatments (anything from supplements, other medications, or other kinds of treatment like prone positioning).

If a treatment is effective early, there is no reason to expect it will also work late. Antivirals are typically only considered effective when used within a short timeframe, for example 0-36 or 0-48 hours for oseltamivir, with longer delays not being effective ***[McLean, Treanor]***. For HCQ, the overwhelming majority of trials involve treatment not only after 48 hours but after 5 days - results from these trials are not relevant to earlier usage.

Authors desiring to produce a negative outcome for HCQ need only focus on late treatment studies. For example, ***[Axfors]*** assigns 89% weight to the RECOVERY and SOLIDARITY trials, producing the same negative result. These trials used excessively high non-patient-customized dosage in very sick late stage patients, dosages comparable to those known to be harmful in that context ***[Borba]***. The results are not generalizable to typical dosage or treatment of earlier stage hospitalized patients, and certainly not applicable to early treatment, i.e., at first glance we can see that this meta analysis is of no relevance to early treatment.

This paper also does not appear to have been done very carefully. For example, authors include ***[Borba]*** which is assigned 97% weight for CQ. This study has no control group, comparing two different dosages of CQ, which is clear from the abstract of the study.

[Axfors] approximate early treatment with outpatient use, where they list 5 trials. This is misleading because authors ignore all outcomes other than mortality, and only one of the 5 trials has mortality events, so in reality only one trial is included. Table 1 shows the 5 trials, only one with mortality. The text says something different: "among the five studies on outpatients, there were three deaths, two occurring in the one trial of 491 relatively young patients with few comorbidities and one occurring in a small trial with 27 patients". We do not know what the missing 27 patient trial is, none of the 5 outpatient trials in Table 1 show 27 patients. There is an outpatient trial with 27 patients ***[Amaravadi]***, however that trial reports no mortality. It does appear in the meta analysis, but is reported as being an inpatient trial with

zero mortality (in reality it was a remotely conducted trial of patients quarantined at home). The supplementary appendix has another different version for outpatient trials, with only 4 trials in Table S3 and Figure S2B (only one with mortality).

Therefore, of the 38 early treatment trials, authors have included data from only one, which contains only 1 death in each of the treatment and control groups. If we read the actual study ***[Skipper]***, we find that the death in the treatment group was a non-hospitalized patient, suggesting that the death was not caused by COVID-19, or at a minimum the patient did not receive standard care and the comparison here is therefore not valid.

Conclusion

HCQ is an effective treatment for COVID-19. Treatment is more effective when used early. Meta analysis using the most serious outcome reported shows 63% [53-70%] improvement for the 38 early treatment studies. Results are similar after exclusion based sensitivity analysis and after restriction to peer-reviewed studies. Restricting to the 11 RCTs shows 39% [8-59%] improvement, and restricting to the 15 mortality results shows 72% [57-81%] lower mortality. Very late stage treatment is not effective and may be harmful, especially when using excessive dosages.

Revisions

This paper is data driven, all graphs and numbers are dynamically generated. We will update the paper as new studies are released or with any corrections. Please submit updates and corrections at https://hcqmeta.com/.

6/5: We added ***[Tu]***.

6/1: We added ***[Satti]***.

5/21: We added ***[Shaw]***.

5/21: We added ***[Silva]***.

5/11: We added ***[Niwas]***.

5/9: We added ***[Uyaroğlu]***.

5/6: We added ***[Hong]***.

5/3: We updated ***[Kadnur]*** to the journal version.

5/2: We added ***[MacFadden]***.

4/17: We added a section on preclinical research.

4/16: We added ***[Roy-García]***.

4/13: We added ***[Rosenthal]***.

4/9: We added *[Hafez]*.

3/31: We added *[Avezum]*.

3/26: We added *[Salehi]*.

3/26: We added *[Oztas]*.

3/26: We added *[Schmidt]*.

3/25: We added *[AlQahtani]*.

3/23: We added *[Opdam]*.

3/21: We added *[Arabi]*.

3/19: We added *[Ebongue]*.

3/10: We added *[Azaña Gómez]*.

3/8: We added *[Cortez]*.

3/6: We added *[Khoubnasabjafari]*.

3/5: We added *[Del Amo, Tsanovska]*.

3/4: We added *[Soto (B)]*.

3/3: We added *[Lavilla Olleros]*.

3/3: We updated *[Beltran Gonzalez]* to the journal version.

3/1: We added *[Alwafi]*.

2/26: We added *[Rouamba]*.

2/22: We updated *[Ader]* with the new results released 2/21/2022.

2/23: We added *[Omma]*.

2/22: We added *[Tamura (B)]*.

2/21: We added *[Cordtz, Ugarte-Gil]*.

2/20: We added *[Mahale]*.

2/16: We added *[Mahto]*.

2/14: We added *[Beaumont]*.

2/7: We added *[Karruli]*.

2/6: We added *[Belmont]*.

2/5: We added *[Erden]*.

2/4: We added *[Albanghali]*.

1/30: We added *[Haji Aghajani]*.

1/24: We added *[Corradini]*.

1/21: We added *[AbdelGhaffar]*.

1/14: We added *[Juneja]*.

1/13: We added *[Atipornwanich]*. We added identification for combined treatment, comparison with other treatments, and use of CQ in Figure 1.

1/10/2022: We updated *[Syed]* to the journal version.

12/23: We added *[McKinnon]*.

12/14: We noted that the majority of the PrEP studies reporting negative effects are studies where all or most patients were autoimmune disorder patients *[Crawford]*.

12/12: We added *[Rao]*.

12/11: We added *[Calderón]*.

12/5: We added *[Ferreira]*.

12/4: We added *[Ahmed]*.

12/4: We updated *[Grau-Pujol]* to the journal version.

11/18: We added *[Samajdar]*.

11/7: We added *[Chechter]*.

11/3: We added *[Guglielmetti (B), Sarhan]*.

10/19: We added a summary plot for all results.

10/12: We added *[Menardi]*.

10/10: We added *[Luo (B)]*.

10/4: We added *[Fung]*.

10/4: We added *[Babalola]*.

9/29: We corrected a display error causing some points to be missing in Figure 4.

9/27: We added *[Uygen]*, and updated *[Million]* to the journal version.

9/19: We added *[Alotaibi, Çivriz Bozdağ]*.

9/17: We added *[Çiyiltepe]*.

9/15: We added *[Agarwal]*.

9/14: We added *[Sawanpanyalert]*.

9/14: We added *[Mulhem]*.

9/12: We added *[Küçükakkaş]*.

9/9: We added *[Alhamlan]*.

9/7: Discussion updates.

8/28: We added *[Patil]*.

8/27: We added *[Rodrigues]*.

8/25: We added *[Naggie]*.

8/21: We added *[Gadhiya]*.

8/20: We corrected the event counts in *[Berenguer]*.

8/17: We added *[De Luna]*.

8/16: We added *[Turrini]*.

8/12: We added *[Shabani]*.

8/10: We added *[Rogado]*.

8/8: We added *[Di Castelnuovo]*.

8/7: We added *[Datta, Kadnur]*.

8/6: We added *[Yadav (B)]*.

8/5: We added *[Bhatt]*.

8/4: We added *[Alghamdi]*.

8/3: We added *[Barra]*.

7/30: We updated *[Bosaeed]* to the journal version, and added *[Sobngwi]*.

7/19: We added analysis restricted to hospitalization results.

7/15: We added *[Jacobs]*.

7/14: We added *[Roger]*.

7/13: We added *[Barrat-Due]*.

7/11: We added ***[Krishnan]***.

7/8: We updated ***[Cadegiani]*** to the journal version.

7/2: We added ***[Taieb]***.

6/22: We added ***[Schwartz]***.

6/21: We added ***[Ramírez-García]***.

6/16: We added ***[Saib]***.

6/12: We added ***[Sivapalan]***.

6/8: We added ***[Burdick, Singh (B)]***.

6/7: We added ***[Badyal]***.

6/6: We added ***[Lagier]***.

6/5: We added ***[Thompson]***.

6/4: We added ***[Byakika-Kibwika, Korkmaz]***.

6/2: We added ***[Kamstrup, Smith]***.

5/28: We added ***[Million]***.

5/17: We added ***[Syed]***.

5/16: We added ***[Rojas-Serrano]***. We corrected the group sizes for ***[Skipper]***, and we excluded hospitalizations that were reported as not being related to COVID-19.

5/15: We added ***[Sammartino]***.

5/14: We added more discussion of heterogeneity.

5/12: We added ***[De Rosa]***.

5/10: We added additional information in the abstract.

5/8: We added ***[Réa-Neto]***.

5/7: We added ***[Kokturk]***.

5/3: We added an explanation of how some meta analyses produce negative results.

5/4: We added ***[Aghajani]***.

5/1: We added ***[Bosaeed]***.

4/29: We added ***[Mohandas]***.

4/23: We added ***[Reis]***.

4/20: We added *[Alegiani, Alzahrani]*.

4/14: We added *[Seet]*.

4/9: We updated *[Dubee]* to the journal version.

4/6: We added *[Mokhtari]*.

4/4: We updated *[Mitjà]* for 11 control hospitalizations. There is conflicting data, table S2 lists 12 control hospitalizations, while table 2 shows 11. A previous version of this paper also showed some values corresponding to 12 control hospitalizations in the abstract and table 2.

4/2: We added *[Salvarani]*.

4/1: We added *[Alghamdi (B)]*.

3/29: We added *[Barry]*.

3/28: We added *[Stewart]*.

3/27: We added *[Hraiech]*, and we corrected an error in effect extraction for *[Self]*.

3/24: We added *[Dev]*.

3/13: We added *[Roy]*.

3/9: We added *[Vivanco-Hidalgo]*.

3/8: We added *[Martin-Vicente]*.

3/7: We added *[Salvador]*.

3/5: We added *[Lotfy]*.

3/3: We added *[Pasquini]*.

3/2: We added *[Pham]*.

2/28: We added *[Rodriguez]*.

2/26: We added *[Amaravadi]*.

2/23: We added *[Beltran Gonzalez]*.

2/25: We added *[Bae]*.

2/20: We added *[Lamback]*.

2/18: We added *[Awad]*.

2/17: We added *[Purwati (B)]*.

2/16: We added *[Albani]*.

2/15: We added *[Lora-Tamayo]*.

2/10: We added *[Roig, Ubaldo]*.

2/9: We added *[Ouedraogo]*.

2/7: We added *[Johnston]*.

2/6: We added *[Fitzgerald]*.

2/5: We added *[Hernandez-Cardenas]*.

2/2: We added *[Bernabeu-Wittel]*.

2/1: We added *[Trefond]*.

1/24: We added *[Desbois, Psevdos]*. We moved the analysis with exclusions and mortality analysis to the main text.

1/21: We added *[Li]*.

1/16: We added the effect measured for each study in the forest plots.

1/15: We updated *[Ip]* to the published version.

1/12: We added *[Li (B)]*.

1/11: We added *[Rangel]*.

1/9: We added *[Texeira, Yegerov]*.

1/7: We added direct links to the study details in the chronological plots.

1/6: We added direct links to the study details in the forest plots.

1/5: We added *[Sarfaraz]*.

1/4: We added *[Vernaz]*.

1/3: We added dosage information for early treatment studies.

1/2: We added the number of patients to the forest plots.

1/1/2021: We added *[Sands]*.

12/31: We added additional details about the studies in the appendix.

12/29: We added *[Güner, Salazar]*.

12/28: We added *[Auld, Cordtz (B)]*.

12/27: We added the total number of authors and patients.

12/25: We added *[Chari]*.

12/24: We added *[Su]*.

12/23: We added *[Cangiano]*.

12/22: We added *[Taccone]*.

12/21: We added *[Matangila]*.

12/20: We added *[Gönenli, Huh]*.

12/17: We added *[Signes-Costa]*.

12/16: We added *[Alqassieh, Naseem, Orioli, Sosa-García, Tan]*.

12/15: We added *[Kalligeros, López]*.

12/14: We added *[Rivera-Izquierdo, Rodriguez-Nava]*.

12/13: We added *[Bielza]*.

12/11: We added *[Jung]*.

12/9: We added *[Agusti, Guglielmetti (B)]*.

12/8: We added *[Barnabas]*.

12/7: We added *[Maldonado]*.

12/4: We added *[Modrák, Ozturk, Peng]*.

12/2: We added *[Rodriguez-Gonzalez]*.

12/1: We added *[Capsoni]*.

11/30: We added *[Abdulrahman]*.

11/28: We added *[Lambermont]*.

11/27: We added *[van Halem]*.

11/25: We added *[Qin]*, and we added analysis restricted to mortality results.

11/24: We added *[Boari]*.

11/23: We added *[Revollo]*.

11/20: We added *[Omrani]*.

11/19: We added *[Falcone]*.

11/18: We added *[Budhiraja]*.

11/14: We added *[Sheshah]*.

11/13: We added ***[Núñez-Gil, Águila-Gordo]***.

11/12: We added ***[Simova, Simova (B)]***.

11/10: We added ***[Mathai]***.

11/9: We added ***[Self]***.

11/8: We added ***[Dhibar]***.

11/4: We added ***[Behera, Cadegiani]***.

11/1: We added ***[Trullàs]***.

10/31: We added ***[Frontera, Szente Fonseca, Tehrani]***.

10/30: We added ***[Berenguer, Faíco-Filho]***.

10/28: We added ***[Arleo, Choi]***.

10/26: We added ***[Coll, Goenka, Synolaki]***.

10/23: We added ***[Komissarov, Lano]***. The second version of the preprint for ***[Komissarov]*** includes a comparison with the control group (not reported in the first version). We updated ***[Lyngbakken]*** to use the mortality result in the recent journal version of the paper (not reported in the preprint).

10/22: We added ***[Anglemyer, Ñamendys-Silva]***. We updated the discussion of ***[Axfors]*** for the second version of this study. We added a table summarizing RCT results.

10/21: We added studies ***[Dubee, Martinez-Lopez, Solh]***. We received a report that the United States National Institutes of Health is recommending against HCQ for hospitalized and non-hospitalized patients as of October 9, and we added a reference.

10/20/2020: Initial revision.

Appendix 1. Methods and Data

We performed ongoing searches of PubMed, medRxiv, ClinicalTrials.gov, The Cochrane Library, Google Scholar, Collabovid, Research Square, ScienceDirect, Oxford University Press, the reference lists of other studies and meta-analyses, and submissions to the site c19hcq.com, which regularly receives submissions of both positive and negative studies upon publication. Search terms were hydroxychloroquine or chloroquine and COVID-19 or SARS-CoV-2, or simply hydroxychloroquine or chloroquine. Automated searches are performed every hour with notifications of new matches. All studies regarding the use of HCQ or CQ for COVID-19 that report a result compared to a control group are included in the main analysis. This is a living analysis and is updated regularly.

We extracted effect sizes and associated data from all studies. If studies report multiple kinds of effects then the most serious outcome is used in calculations for that study. For example, if effects for mortality and cases are both reported, the effect for mortality is used, this may be different to the effect that a study focused on. If symptomatic results are reported at multiple times, we used the latest time, for example if mortality results are provided at 14 days and 28 days, the results at 28 days are used.

Mortality alone is preferred over combined outcomes. Outcomes with zero events in both arms were not used (the next most serious outcome is used — no studies were excluded). For example, in low-risk populations with no mortality, a reduction in mortality with treatment is not possible, however a reduction in hospitalization, for example, is still valuable. Clinical outcome is considered more important than PCR testing status. When basically all patients recover in both treatment and control groups, preference for viral clearance and recovery is given to results mid-recovery where available (after most or all patients have recovered there is no room for an effective treatment to do better). When results provide an odds ratio, we computed the relative risk when possible, or converted to a relative risk according to ***[Zhang]***. Reported confidence intervals and *p*-values were used when available, using adjusted values when provided. If multiple types of adjustments are reported including propensity score matching (PSM), the PSM results are used. Adjusted primary outcome results have preference over unadjusted results for a more serious outcome when the adjustments significantly alter results. When needed, conversion between reported *p*-values and confidence intervals followed ***[Altman, Altman (B)]***, and Fisher's exact test was used to calculate *p*-values for event data. If continuity correction for zero values is required, we use the reciprocal of the opposite arm with the sum of the correction factors equal to 1 ***[Sweeting]***. If a study separates HCQ and HCQ+AZ, we use the combined results were possible, or the results for the larger group. Results are all expressed with RR < 1.0 suggesting effectiveness. Most results are the relative risk of something negative. If a study reports relative times, the results are expressed as the ratio of the time for the HCQ group versus the time for the control group. If a study reports the rate of reduction of viral load, the results are based on the percentage change in the rate. Calculations are done in Python (3.9.13) with scipy (1.8.0), pythonmeta (1.26), numpy (1.22.2), statsmodels (0.14.0), and plotly (5.6.0).

The forest plots are computed using PythonMeta ***[Deng]*** with the DerSimonian and Laird random effects model (the fixed effect assumption is not plausible in this case).

We received no funding, this research is done in our spare time. We have no affiliations with any pharmaceutical companies or political parties.

We have classified studies as early treatment if most patients are not already at a severe stage at the time of treatment, and treatment started within 5 days after the onset of symptoms, although a shorter time may be preferable. Antivirals are typically only considered effective when used within a shorter timeframe, for example 0-36 or 0-48 hours for oseltamivir, with longer delays not being effective ***[McLean, Treanor]***.

A summary of study results is below. Please submit updates and corrections at https://hcqmeta.com/.

Early treatment

Effect extraction follows pre-specified rules as detailed above and gives priority to more serious outcomes. Only the first (most serious) outcome is used in pooled analysis, which may differ from the effect a paper focuses on. Other outcomes are used in outcome specific analyses.

[Agusti], 12/9/2020, prospective, Spain, Europe, peer-reviewed, median age 37.0, 13 authors, average treatment delay 5.0 days, dosage 400mg bid day 1, 200mg bid days 2-5.	risk of progression, 68.4% lower, RR 0.32, *p* = 0.21, treatment 2 of 87 (2.3%), control 4 of 55 (7.3%), NNT 20, pneumonia.
[Amaravadi], 2/26/2021, Double Blind Randomized Controlled Trial, USA, North	risk of not reaching lowest symptom score at day 7 mid-recovery, 60.0% lower, RR 0.40, *p* = 0.13,

America, preprint, 20 authors, dosage 400mg bid days 1-14.	treatment 3 of 15 (20.0%), control 6 of 12 (50.0%), NNT 3.3.
	relative time to first occurrence of lowest symptom score, 42.9% lower, relative time 0.57, p = 0.21, treatment 15, control 12.
	relative time to release from quarantine, 27.3% lower, relative time 0.73, p = 0.28, treatment 16, control 13.
[Ashraf], 4/24/2020, retrospective, database analysis, Iran, Middle East, preprint, median age 58.0, 16 authors, dosage 200mg bid daily, 400mg qd was used when combined with Lopinavir-Ritonavir.	risk of death, 67.5% lower, RR 0.32, p = 0.15, treatment 10 of 77 (13.0%), control 2 of 5 (40.0%), NNT 3.7.
[Atipornwanich], 10/5/2021, Randomized Controlled Trial, Thailand, South Asia, peer-reviewed, 16 authors, early treatment subset, dosage 400mg days 1-14, 800mg/day or 400mg/day, this trial compares with another treatment - results may be better when compared to placebo, this trial uses multiple treatments in the treatment arm (combined with oseltamivir/favipiravir and duranivir/ritonavir for moderate/severe, oseltamivir and duranivir/ritonavir for mild) - results of individual treatments may vary, trial NCT04303299.	risk of progression, 150.0% higher, RR 2.50, p = 1.00, treatment 1 of 60 (1.7%), control 0 of 30 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm), mild, early treatment result.
	time to viral-, 43.3% lower, relative time 0.57, p = 0.04, treatment mean 8.9 (±6.0) n=30, control mean 15.7 (±16.7) n=30, mild, HCQ 800, primary outcome, early treatment result.
	time to viral-, 36.3% lower, relative time 0.64, p = 0.09, treatment mean 10.0 (±6.9) n=30, control mean 15.7 (±16.7) n=30, mild, HCQ 400, primary outcome, early treatment result.
[Avezum], 3/31/2022, Double Blind Randomized Controlled Trial, Brazil, South America, peer-reviewed, 40 authors, study period 12 May, 2020 - 7 July, 2021, average treatment delay 4.0 days, dosage 400mg bid day 1, 200mg bid days 2-7, trial NCT04466540.	risk of death, 0.7% lower, RR 0.99, p = 1.00, treatment 5 of 687 (0.7%), control 5 of 682 (0.7%), NNT 18741, all-cause death.
	risk of death, 56.0% higher, HR 1.56, p = 0.54, treatment 5 of 687 (0.7%), control 5 of 682 (0.7%), adjusted per study, univariate Firth's penalized likelihood.
	risk of mechanical ventilation, 32.4% higher, RR 1.32, p = 0.79, treatment 8 of 687 (1.2%), control 6 of 682 (0.9%).
	risk of ICU admission, 16.4% lower, RR 0.84, p = 0.61, treatment 16 of 687 (2.3%), control 19 of 682 (2.8%), NNT 219.

	risk of hospitalization, 23.5% lower, RR 0.77, p = 0.18, treatment 44 of 689 (6.4%), control 57 of 683 (8.3%), NNT 51.
	risk of hospitalization, 40.0% lower, RR 0.60, p = 0.15, treatment 267, control 265, <4 days.
[Bernabeu-Wittel], 8/1/2020, retrospective, Spain, Europe, peer-reviewed, 13 authors, dosage 400mg bid day 1, 200mg bid days 2-7, this trial uses multiple treatments in the treatment arm (combined with lopinavir/ritonavir and antimicrobial treatments) - results of individual treatments may vary.	**risk of death, 59.0% lower, RR 0.41, p = 0.03**, treatment 189, control 83.
[Cadegiani], 11/4/2020, prospective, Brazil, South America, peer-reviewed, 4 authors, average treatment delay 2.9 days, dosage 400mg days 1-5.	**risk of death, 81.2% lower, RR 0.19, p = 0.21**, treatment 0 of 159 (0.0%), control 2 of 137 (1.5%), NNT 68, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), control group 1.
	risk of mechanical ventilation, 95.1% lower, RR 0.05, p < 0.001, treatment 0 of 159 (0.0%), control 9 of 137 (6.6%), NNT 15, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), control group 1.
	risk of hospitalization, 98.3% lower, RR 0.02, p < 0.001, treatment 0 of 159 (0.0%), control 27 of 137 (19.7%), NNT 5.1, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), control group 1.
[Chechter], 11/5/2021, prospective, Brazil, South America, preprint, 13 authors, dosage 800mg day 1, 400mg days 2-5, this trial uses multiple treatments in the treatment arm (combined with AZ) - results of individual treatments may vary, excluded in exclusion analyses: unadjusted results with no group details.	**risk of hospitalization, 94.7% lower, RR 0.05, p = 0.004**, treatment 0 of 60 (0.0%), control 3 of 12 (25.0%), NNT 4.0, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
[Chen], 6/22/2020, Randomized Controlled Trial, China, Asia, preprint, 19 authors, dosage 200mg bid days 1-10.	**median time to PCR-, 72.0% lower, relative time 0.28, p = 0.01**, treatment 18, control 12.
[Corradini], 4/24/2021, retrospective, Italy, Europe, peer-reviewed, 60 authors, early	**risk of death, 67.4% lower, OR 0.33, p = 0.01**, treatment 641, control 102, adjusted per study, Table

treatment subset, dosage not specified.	S6, light condition patients, multivariable, RR approximated with OR, early treatment result.
[Derwand], 7/3/2020, retrospective, USA, North America, peer-reviewed, 3 authors, average treatment delay 4.0 days, dosage 200mg bid days 1-5, this trial uses multiple treatments in the treatment arm (combined with AZ and zinc) - results of individual treatments may vary.	**risk of death, 79.4% lower, RR 0.21, p = 0.12**, treatment 1 of 141 (0.7%), control 13 of 377 (3.4%), NNT 37, odds ratio converted to relative risk.
	risk of hospitalization, 81.6% lower, RR 0.18, p < 0.001, treatment 4 of 141 (2.8%), control 58 of 377 (15.4%), NNT 8.0, odds ratio converted to relative risk.
[Esper], 4/15/2020, prospective, Brazil, South America, preprint, 15 authors, average treatment delay 5.2 days, dosage 800mg day 1, 400mg days 2-7, this trial uses multiple treatments in the treatment arm (combined with AZ) - results of individual treatments may vary.	**risk of hospitalization, 64.0% lower, RR 0.36, p = 0.02**, treatment 8 of 412 (1.9%), control 12 of 224 (5.4%), NNT 29.
[Gautret], 3/17/2020, prospective, France, Europe, peer-reviewed, 18 authors, average treatment delay 4.1 days, dosage 200mg tid days 1-10, excluded in exclusion analyses: excessive unadjusted differences between groups, results only for PCR status which may be significantly different to symptoms.	**risk of no virological cure at day 6, 66.0% lower, RR 0.34, p = 0.001**, treatment 6 of 20 (30.0%), control 14 of 16 (87.5%), NNT 1.7.
[Guisado-Vasco], 10/15/2020, retrospective, Spain, Europe, peer-reviewed, median age 69.0, 25 authors, early treatment subset, dosage not specified.	**risk of death, 66.9% lower, RR 0.33, p = 0.19**, treatment 2 of 65 (3.1%), control 139 of 542 (25.6%), NNT 4.4, adjusted per study, odds ratio converted to relative risk, multivariate.
[Guérin], 5/31/2020, retrospective, France, Europe, peer-reviewed, 8 authors, dosage 600mg days 1-10, 7-10 days, this trial uses multiple treatments in the treatment arm (combined with AZ) - results of individual treatments may vary.	**risk of death, 61.4% lower, RR 0.39, p = 1.00**, treatment 0 of 20 (0.0%), control 1 of 34 (2.9%), NNT 34, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	recovery time, 65.0% lower, relative time 0.35, p < 0.001, treatment 20, control 34.
[Heras], 9/2/2020, retrospective, Andorra, Europe, peer-reviewed, median age 85.0, 13 authors, dosage not specified, this trial uses multiple treatments in the treatment arm (combined with AZ) - results of individual treatments may vary.	**risk of death, 95.6% lower, RR 0.04, p = 0.004**, treatment 8 of 70 (11.4%), control 16 of 30 (53.3%), NNT 2.4, adjusted per study.

[Hong], 7/16/2020, retrospective, South Korea, Asia, peer-reviewed, 7 authors, dosage not specified.	**risk of prolonged viral shedding, early vs. late HCQ, 64.9% lower, RR 0.35, p = 0.001**, treatment 42, control 48, odds ratio converted to relative risk.
[Huang (B)], 5/28/2020, prospective, China, Asia, peer-reviewed, 36 authors, early treatment subset, dosage chloroquine 500mg days 1-10, two groups, 500mg qd and 500mg bid.	**time to viral-, 59.1% lower, relative time 0.41, p < 0.001**, treatment 32, control 37.
[Huang (C)], 4/1/2020, Randomized Controlled Trial, China, Asia, peer-reviewed, 18 authors, average treatment delay 2.5 days, dosage chloroquine 500mg bid days 1-10, this trial compares with another treatment - results may be better when compared to placebo.	**risk of no recovery at day 14, 91.7% lower, RR 0.08, p = 0.02**, treatment 0 of 10 (0.0%), control 6 of 12 (50.0%), NNT 2.0, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of no improvement in pneumonia at day 14, 83.0% lower, RR 0.17, p = 0.22, treatment 10, control 12.
[Ip], 8/25/2020, retrospective, database analysis, USA, North America, peer-reviewed, 25 authors, dosage not specified.	**risk of death, 54.5% lower, RR 0.45, p = 0.43**, treatment 2 of 97 (2.1%), control 44 of 970 (4.5%), NNT 40.
	risk of ICU admission, 28.6% lower, RR 0.71, p = 0.79, treatment 3 of 97 (3.1%), control 42 of 970 (4.3%), NNT 81.
	risk of hospitalization, 37.3% lower, RR 0.63, p = 0.04, treatment 21 of 97 (21.6%), control 305 of 970 (31.4%), NNT 10, adjusted per study, odds ratio converted to relative risk.
[Kirenga], 9/9/2020, prospective, Uganda, Africa, peer-reviewed, 29 authors, dosage not specified.	**median time to recovery, 25.6% lower, relative time 0.74, p = 0.20**, treatment 29, control 27.
[Ly], 8/21/2020, retrospective, France, Europe, peer-reviewed, mean age 83.0, 21 authors, dosage 200mg tid days 1-10, this trial uses multiple treatments in the treatment arm (combined with AZ) - results of individual treatments may vary.	**risk of death, 55.6% lower, RR 0.44, p = 0.02**, treatment 18 of 116 (15.5%), control 29 of 110 (26.4%), NNT 9.2, adjusted per study, odds ratio converted to relative risk.
[Million], 5/27/2021, retrospective, France, Europe, peer-reviewed, 28 authors, average treatment delay 4.0 days, dosage 200mg tid days 1-10, this trial uses multiple	**risk of death, 83.0% lower, HR 0.17, p < 0.001**, treatment 5 of 8,315 (0.1%), control 11 of 2,114 (0.5%), NNT 217, adjusted per study.
	risk of ICU admission, 44.0% lower, HR 0.56, p = 0.18,

treatments in the treatment arm (combined with AZ) - results of individual treatments may vary.	treatment 17 of 8,315 (0.2%), control 7 of 2,114 (0.3%), NNT 789, adjusted per study.
	risk of hospitalization, 4.0% lower, HR 0.96, *p* = 0.77, treatment 214 of 8,315 (2.6%), control 64 of 2,114 (3.0%), adjusted per study.
[Mitjà], 7/16/2020, Randomized Controlled Trial, Spain, Europe, peer-reviewed, 45 authors, dosage 800mg day 1, 400mg days 2-7.	**risk of hospitalization, 16.0% lower, RR 0.84, *p* = 0.64**, treatment 8 of 136 (5.9%), control 11 of 157 (7.0%), NNT 89.
	risk of no recovery, 34.0% lower, RR 0.66, *p* = 0.38, treatment 8 of 136 (5.9%), control 14 of 157 (8.9%), NNT 33.
[Mokhtari], 4/6/2021, retrospective, Iran, Middle East, peer-reviewed, 11 authors, dosage 400mg bid day 1, 200mg bid days 2-5.	**risk of death, 69.7% lower, RR 0.30, *p* < 0.001**, treatment 27 of 7,295 (0.4%), control 287 of 21,464 (1.3%), NNT 103, adjusted per study, odds ratio converted to relative risk.
	risk of hospitalization, 35.3% lower, RR 0.65, *p* < 0.001, treatment 523 of 7,295 (7.2%), control 2,382 of 21,464 (11.1%), NNT 25, adjusted per study, odds ratio converted to relative risk.
[Omrani], 11/20/2020, Randomized Controlled Trial, Qatar, Middle East, peer-reviewed, 19 authors, dosage 600mg days 1-6, this trial uses multiple treatments in the treatment arm (combined with AZ) - results of individual treatments may vary.	**risk of hospitalization, 12.5% lower, RR 0.88, *p* = 1.00**, treatment 7 of 304 (2.3%), control 4 of 152 (2.6%), NNT 304, HCQ+AZ or HCQ vs. control.
	risk of symptomatic at day 21, 25.8% lower, RR 0.74, *p* = 0.58, treatment 9 of 293 (3.1%), control 6 of 145 (4.1%), NNT 94, HCQ+AZ or HCQ vs. control.
	risk of Ct<=40 at day 14, 10.3% higher, RR 1.10, *p* = 0.13, treatment 223 of 295 (75.6%), control 98 of 143 (68.5%), HCQ+AZ or HCQ vs. control.
[Rodrigues], 8/25/2021, Double Blind Randomized Controlled Trial, Brazil, South America, peer-reviewed, 8 authors, average treatment delay 3.8 days, dosage 400mg bid days 1-7, this trial uses multiple treatments in the treatment arm (combined with AZ) - results of individual treatments may vary.	**risk of hospitalization, 200.0% higher, RR 3.00, *p* = 1.00**, treatment 1 of 42 (2.4%), control 0 of 42 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm).
	risk of no viral clearance, 14.4% lower, RR 0.86, *p* = 0.15, treatment 29 of 36 (80.6%), control 32 of 34 (94.1%), NNT 7.4, PP, day 3.
	risk of no viral clearance, 13.1% lower, RR 0.87, *p* = 0.45, treatment 23 of 36 (63.9%), control 25 of 34 (73.5%), NNT 10, PP, day 6.

	risk of no viral clearance, 23.3% lower, RR 0.77, *p* = 0.47, treatment 13 of 36 (36.1%), control 16 of 34 (47.1%), NNT 9.1, PP, day 9.
	risk of no viral clearance, 3.1% lower, RR 0.97, *p* = 1.00, treatment 31 of 42 (73.8%), control 32 of 42 (76.2%), NNT 42, ITT, day 3.
	risk of no viral clearance, no change, RR 1.00, *p* = 1.00, treatment 25 of 42 (59.5%), control 25 of 42 (59.5%), ITT, day 6.
	risk of no viral clearance, 6.2% lower, RR 0.94, *p* = 1.00, treatment 15 of 42 (35.7%), control 16 of 42 (38.1%), NNT 42, ITT, day 9.
	time to viral-, 8.8% lower, relative time 0.91, *p* = 0.26, treatment 36, control 34, PP.
	time to viral-, 1.4% lower, relative time 0.99, *p* = 0.85, treatment 42, control 42, ITT.
[Rouamba], 2/26/2022, retrospective, Burkina Faso, Africa, peer-reviewed, mean age 42.2, 17 authors, early treatment subset, study period 9 March, 2020 - 31 October, 2020, dosage 200mg tid days 1-10, HCQ 200mg tid daily or CQ 250mg bid daily, trial NCT04445441.	**risk of progression, 73.0% lower, HR 0.27, *p* = 0.05**, treatment 23 of 399 (5.8%), control 4 of 33 (12.1%), adjusted per study, outpatients, multivariable, Cox proportional hazards, early treatment result.
	time to viral clearance, 21.3% lower, HR 0.79, *p* = 0.37, treatment 399, control 33, adjusted per study, outpatients, multivariable, Cox proportional hazards, primary outcome, early treatment result.
[Roy], 3/12/2021, retrospective, database analysis, India, South Asia, preprint, 5 authors, dosage not specified, excluded in exclusion analyses: no serious outcomes reported and fast recovery in treatment and control groups, there is little room for a treatment to improve results.	**relative time to clinical response of wellbeing, 2.4% lower, relative time 0.98, *p* = 0.96**, treatment 14, control 15, primary outcome.
[Roy-García], 4/16/2022, Double Blind Randomized Controlled Trial, Mexico, North America, preprint, 11 authors, average treatment delay 5.0 days, dosage 200mg bid days 1-10, trial NCT04964583.	**risk of progression, 100% higher, RR 2.00, *p* = 1.00**, treatment 2 of 31 (6.5%), control 1 of 31 (3.2%), supplemental oxygen.
	risk of progression, 233.3% higher, RR 3.33, *p* = 0.06, treatment 10 of 31 (32.3%), control 3 of 31 (9.7%), pneumonia.
	risk of progression, 225.0% higher, RR 3.25, *p* = 0.02,

	treatment 13 of 31 (41.9%), control 4 of 31 (12.9%), oxygen saturation less than 90%, dyspnea, or pneumonia.
[Sawanpanyalert], 9/9/2021, retrospective, Thailand, South Asia, peer-reviewed, 11 authors, dosage varies, this trial uses multiple treatments in the treatment arm (combined with lopinavir/ritonavir or darunavir/ritonavir) - results of individual treatments may vary.	**risk of death, ICU, intubation, or high-flow oxygen, 42.0% lower, OR 0.58, *p* = 0.37**, within 4 days of symptom onset, RR approximated with OR.
[Simova], 11/12/2020, retrospective, Bulgaria, Europe, peer-reviewed, 5 authors, dosage 200mg tid days 1-14, this trial uses multiple treatments in the treatment arm (combined with AZ and zinc) - results of individual treatments may vary.	**risk of hospitalization, 93.8% lower, RR 0.06, *p* = 0.01**, treatment 0 of 33 (0.0%), control 2 of 5 (40.0%), NNT 2.5, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of viral+ at day 14, 95.8% lower, RR 0.04, *p* = 0.001, treatment 0 of 33 (0.0%), control 3 of 5 (60.0%), NNT 1.7, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
[Skipper], 7/16/2020, Randomized Controlled Trial, USA, North America, peer-reviewed, 24 authors, dosage 800mg once, followed by 600mg in 6 to 8 hours, then 600mg daily for 4 more days, trial NCT04308668.	**risk of death/hospitalization, 36.7% lower, RR 0.63, *p* = 0.58**, treatment 5 of 231 (2.2%), control 8 of 234 (3.4%), NNT 80, COVID-19 adjudicated hospitalization/death.
	risk of hospitalization, 49.4% lower, RR 0.51, *p* = 0.38, treatment 4 of 231 (1.7%), control 8 of 234 (3.4%), NNT 59, COVID-19 adjudicated hospitalization.
	risk of death/hospitalization, 49.4% lower, RR 0.51, *p* = 0.29, treatment 5 of 231 (2.2%), control 10 of 234 (4.3%), NNT 47, all hospitalization/death.
	risk of hospitalization, 59.5% lower, RR 0.41, *p* = 0.17, treatment 4 of 231 (1.7%), control 10 of 234 (4.3%), NNT 39, all hospitalizations.
	risk of no recovery at day 14, 20.0% lower, RR 0.80, *p* = 0.21, treatment 231, control 234.
[Sobngwi], 7/29/2021, Randomized Controlled Trial, Cameroon, Africa, preprint, 16 authors, dosage 400mg days 1-5, this	**risk of no recovery, 51.6% lower, RR 0.48, *p* = 0.44**, treatment 2 of 95 (2.1%), control 4 of 92 (4.3%), NNT 45, day 10.
	risk of no recovery, 3.2% lower, RR 0.97, *p* = 1.00,

trial compares with another treatment - results may be better when compared to placebo.	treatment 18 of 95 (18.9%), control 18 of 92 (19.6%), NNT 162, day 3.
	risk of no viral clearance, 3.2% lower, RR 0.97, *p* = 0.88, treatment 32 of 95 (33.7%), control 32 of 92 (34.8%), NNT 91, day 10.
[Su], 12/23/2020, retrospective, China, Asia, peer-reviewed, 9 authors, study period 20 January, 2020 - 30 April, 2020, dosage 400mg days 1-10, 400mg daily for 10-14 days.	**risk of progression, 84.9% lower, HR 0.15, *p* = 0.006**, adjusted per study, binary logistic regression.
	improvement time, 24.0% better, relative time 0.76, *p* = 0.02, adjusted per study, Cox proportional hazards.
	risk of no viral clearance, 35.8% lower, HR 0.64, *p* = 0.001, Cox proportional hazards.
[Sulaiman], 9/13/2020, prospective, Saudi Arabia, Middle East, preprint, 22 authors, dosage 400mg bid day 1, 200mg bid days 2-5.	**risk of death, 63.7% lower, RR 0.36, *p* = 0.01**, treatment 7 of 1,817 (0.4%), control 54 of 3,724 (1.5%), NNT 94, adjusted per study, odds ratio converted to relative risk.
	risk of hospitalization, 38.6% lower, RR 0.61, *p* = 0.001, treatment 171 of 1,817 (9.4%), control 617 of 3,724 (16.6%), NNT 14, adjusted per study, odds ratio converted to relative risk.
[Szente Fonseca], 10/31/2020, retrospective, Brazil, South America, peer-reviewed, mean age 50.6, 10 authors, average treatment delay 4.6 days, dosage 400mg bid day 1, 400mg qd days 2-5.	**risk of hospitalization, 64.0% lower, RR 0.36, *p* < 0.001**, treatment 25 of 175 (14.3%), control 89 of 542 (16.4%), adjusted per study, odds ratio converted to relative risk, HCQ vs. nothing, primary outcome.
	risk of hospitalization, 50.5% lower, RR 0.49, *p* = 0.006, treatment 25 of 175 (14.3%), control 89 of 542 (16.4%), adjusted per study, odds ratio converted to relative risk, HCQ vs. anything else.
[Yu], 8/3/2020, retrospective, China, Asia, preprint, median age 62.0, 6 authors, early treatment subset, average treatment delay 5.0 days, dosage 200mg bid days 1-10.	**risk of death, 85.0% lower, RR 0.15, *p* = 0.02**, treatment 1 of 73 (1.4%), control 238 of 2,604 (9.1%), NNT 13, HCQ treatment started early vs. non-HCQ.

Late treatment

Effect extraction follows pre-specified rules as detailed above and gives priority to more serious outcomes. Only the first (most serious) outcome is used in pooled analysis, which may differ from the effect a paper focuses on. Other outcomes are used in outcome specific analyses.

[Abd-Elsalam], 8/14/2020, Randomized	**risk of death, 20.0% higher, RR 1.20, *p* = 1.00**,

Controlled Trial, Egypt, Africa, peer-reviewed, 10 authors.	treatment 6 of 97 (6.2%), control 5 of 97 (5.2%).
	risk of no recovery at day 28, 30.0% lower, RR 0.70, *p* = 0.009, treatment 45 of 97 (46.4%), control 64 of 97 (66.0%), NNT 5.1.
[AbdelGhaffar], 1/11/2022, retrospective, Egypt, Africa, peer-reviewed, 17 authors, study period April 2020 - July 2020.	**risk of death, 99.9% lower, RR 0.001, *p* < 0.001**, treatment 0 of 238 (0.0%), control 900 of 3,474 (25.9%), NNT 3.9, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
[Abdulrahman], 11/30/2020, retrospective, propensity score matching, Bahrain, Middle East, preprint, 9 authors.	**risk of death, 16.7% lower, RR 0.83, *p* = 1.00**, treatment 5 of 223 (2.2%), control 6 of 223 (2.7%), NNT 223, PSM.
	risk of death/intubation, 75.0% higher, RR 1.75, *p* = 0.24, treatment 12 of 223 (5.4%), control 7 of 223 (3.1%), adjusted per study, PSM.
[Ader], 10/6/2020, Randomized Controlled Trial, multiple countries, multiple regions, preprint, baseline oxygen required 95.4%, 59 authors, study period 22 March, 2020 - 29 June, 2020, average treatment delay 9.0 days, excluded in exclusion analyses: very late stage, >50% on oxygen/ventilation at baseline.	**risk of death, 15.3% higher, RR 1.15, *p* = 0.70**, treatment 11 of 150 (7.3%), control 13 of 149 (8.7%), adjusted per study, odds ratio converted to relative risk, day 90.
	risk of death, 10.1% lower, RR 0.90, *p* = 0.75, treatment 15 of 150 (10.0%), control 13 of 149 (8.7%), adjusted per study, odds ratio converted to relative risk, day 28.
	risk of no viral clearance, 23.8% lower, RR 0.76, *p* = 0.68, treatment 4 of 83 (4.8%), control 5 of 81 (6.2%), NNT 74, odds ratio converted to relative risk, Table S2, day 29.
[Aghajani], 4/29/2021, retrospective, Iran, Middle East, peer-reviewed, 7 authors.	**risk of death, 19.5% lower, HR 0.81, *p* = 0.09**, treatment 553, control 438, multivariate Cox proportional regression.
[Alamdari], 9/9/2020, retrospective, Iran, Middle East, peer-reviewed, 14 authors, average treatment delay 5.72 days, excluded in exclusion analyses: substantial unadjusted confounding by indication likely.	**risk of death, 55.0% lower, RR 0.45, *p* = 0.03**, treatment 54 of 427 (12.6%), control 9 of 32 (28.1%), NNT 6.5.
[Albanghali], 2/3/2022, retrospective, Saudi Arabia, Middle East, peer-reviewed, 8 authors, excluded in exclusion analyses:	**risk of death, 34.6% higher, RR 1.35, *p* = 0.46**, treatment 20 of 466 (4.3%), control 11 of 345 (3.2%).

unadjusted results with no group details, substantial unadjusted confounding by indication likely.	
[Albani], 8/30/2020, retrospective, Italy, Europe, peer-reviewed, 11 authors, excluded in exclusion analyses: substantial unadjusted confounding by indication likely, substantial confounding by time likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically.	**risk of death, 18.4% lower, RR 0.82, *p* = 0.15**, treatment 60 of 211 (28.4%), control 172 of 605 (28.4%), adjusted per study, odds ratio converted to relative risk, HCQ vs. neither.
	risk of death, 9.0% higher, RR 1.09, *p* = 0.54, treatment 60 of 211 (28.4%), control 172 of 605 (28.4%), adjusted per study, odds ratio converted to relative risk, HCQ+AZ vs. neither.
	risk of ICU admission, 9.2% higher, RR 1.09, *p* = 0.70, treatment 73 of 211 (34.6%), control 46 of 605 (7.6%), adjusted per study, odds ratio converted to relative risk, HCQ vs. neither.
	risk of ICU admission, 71.3% higher, RR 1.71, *p* < 0.001, treatment 73 of 211 (34.6%), control 46 of 605 (7.6%), adjusted per study, odds ratio converted to relative risk, HCQ+AZ vs. neither.
[Alberici], 5/10/2020, retrospective, Italy, Europe, peer-reviewed, 31 authors, average treatment delay 4.0 days.	**risk of death, 42.9% lower, RR 0.57, *p* = 0.12**, treatment 17 of 72 (23.6%), control 9 of 22 (40.9%), NNT 5.8, odds ratio converted to relative risk.
[Alghamdi], 8/4/2021, retrospective, Saudi Arabia, Middle East, peer-reviewed, 1 author, excluded in exclusion analyses: unadjusted results with no group details, very late stage, ICU patients.	**risk of death, 39.2% higher, RR 1.39, *p* = 0.52**, treatment 29 of 128 (22.7%), control 7 of 43 (16.3%).
[Alghamdi (B)], 3/31/2021, retrospective, Saudi Arabia, Middle East, peer-reviewed, 10 authors, excluded in exclusion analyses: confounding by indication is likely and adjustments do not consider COVID-19 severity at baseline.	**risk of death, 6.9% higher, RR 1.07, *p* = 0.88**, treatment 44 of 568 (7.7%), control 15 of 207 (7.2%).
[Alhamlan], 7/16/2021, retrospective, database analysis, Saudi Arabia, Middle East, preprint, 10 authors, excluded in exclusion analyses: substantial unadjusted confounding by indication likely, substantial confounding by time likely due to declining	**risk of death, 52.0% higher, HR 1.52, *p* = 0.57**.

usage over the early stages of the pandemic when overall treatment protocols improved dramatically.	
[Almazrou], 10/1/2020, retrospective, Saudi Arabia, Middle East, peer-reviewed, 5 authors.	**risk of mechanical ventilation, 65.0% lower, RR 0.35, p = 0.16**, treatment 3 of 95 (3.2%), control 6 of 66 (9.1%), NNT 17.
	risk of ICU admission, 21.0% lower, RR 0.79, p = 0.78, treatment 8 of 95 (8.4%), control 7 of 66 (10.6%), NNT 46.
[Alotaibi], 9/14/2021, retrospective, Saudi Arabia, Middle East, peer-reviewed, 11 authors, this trial compares with another treatment - results may be better when compared to placebo.	**risk of death, 133.5% higher, RR 2.33, p = 0.05**, treatment 193, control 244, multivariate.
[AlQahtani], 3/23/2022, Randomized Controlled Trial, Bahrain, Middle East, peer-reviewed, 13 authors, study period August 2020 - March 2021, trial NCT04387760.	**risk of ICU admission, 23.5% lower, RR 0.76, p = 1.00**, treatment 3 of 51 (5.9%), control 4 of 52 (7.7%), NNT 55.
	risk of no recovery, 4.1% lower, RR 0.96, p = 0.94, treatment 5 of 49 (10.2%), control 5 of 47 (10.6%), NNT 230.
	risk of no viral clearance, 47.4% lower, RR 0.53, p = 0.13, treatment 7 of 38 (18.4%), control 14 of 40 (35.0%), NNT 6.0.
[Alqassieh], 12/10/2020, prospective, Jordan, Middle East, preprint, 10 authors.	**hospitalization time, 18.2% lower, relative time 0.82, p = 0.11**, treatment 63, control 68.
[Alwafi], 1/20/2022, retrospective, Saudi Arabia, Middle East, peer-reviewed, 6 authors, study period 7 March, 2020 - 15 April, 2020, excluded in exclusion analyses: excessive unadjusted differences between groups.	**risk of no viral clearance, 14.7% lower, RR 0.85, p = 0.65**, treatment 12 of 45 (26.7%), control 15 of 48 (31.2%), NNT 22, day 5, primary outcome.
	risk of no viral clearance, 25.3% lower, RR 0.75, p = 0.60, treatment 7 of 45 (15.6%), control 10 of 48 (20.8%), NNT 19, day 12.
[An], 7/7/2020, retrospective, South Korea, Asia, preprint, 12 authors.	**time to viral clearance, 3.0% lower, HR 0.97, p = 0.92**, treatment 31, control 195.
[Annie], 10/12/2020, retrospective, database analysis, USA, North America, peer-reviewed, 5 authors, excluded in	**risk of death, 4.3% lower, RR 0.96, p = 0.83**, treatment 48 of 367 (13.1%), control 50 of 367 (13.6%), NNT 183, odds ratio converted to relative risk.

exclusion analyses: confounding by indication is likely and adjustments do not consider COVID-19 severity at baseline.	risk of death, 20.5% higher, RR 1.21, p = 0.46, treatment 29 of 199 (14.6%), control 24 of 199 (12.1%), odds ratio converted to relative risk.
[Aparisi], 10/8/2020, prospective, Spain, Europe, preprint, 18 authors, excluded in exclusion analyses: unadjusted results with no group details.	**risk of death, 63.0% lower, RR 0.37, p = 0.008**, treatment 122 of 605 (20.2%), control 27 of 49 (55.1%), NNT 2.9.
[Arabi], 7/12/2021, Randomized Controlled Trial, multiple countries, multiple regions, peer-reviewed, 1 author, trial NCT02735707.	**risk of death, 44.5% higher, RR 1.44, p = 0.01**, treatment 17 of 49 (34.7%), control 106 of 353 (30.0%), adjusted per study, odds ratio converted to relative risk, multivariable.
[Arshad], 7/1/2020, retrospective, USA, North America, peer-reviewed, 12 authors.	**risk of death, 51.3% lower, HR 0.49, p = 0.009**, treatment 162 of 1,202 (13.5%), control 108 of 409 (26.4%), NNT 7.7.
[Ashinyo], 9/15/2020, retrospective, Ghana, Africa, peer-reviewed, 16 authors.	**hospitalization time, 33.0% lower, relative time 0.67, p = 0.03**, treatment 61, control 61.
[Atipornwanich], 10/5/2021, Randomized Controlled Trial, Thailand, South Asia, peer-reviewed, 16 authors, dosage 400mg days 1-14, 800mg/day or 400mg/day, this trial compares with another treatment - results may be better when compared to placebo, this trial uses multiple treatments in the treatment arm (combined with oseltamivir/favipiravir and duranivir/ritonavir for moderate/severe, oseltamivir and duranivir/ritonavir for mild) - results of individual treatments may vary, trial NCT04303299.	**risk of death, 56.2% lower, RR 0.44, p = 0.07**, treatment 7 of 100 (7.0%), control 16 of 100 (16.0%), NNT 11, moderate/severe, HCQ arms vs. non-HCQ arms.
	risk of progression, 54.2% lower, RR 0.46, p = 0.02, treatment 11 of 100 (11.0%), control 24 of 100 (24.0%), NNT 7.7, moderate/severe, HCQ arms vs. non-HCQ arms.
	time to viral-, 7.1% lower, relative time 0.93, p = 0.51, treatment mean 10.4 (±6.3) n=50, control mean 11.2 (±5.7) n=50, moderate/severe, oseltamivir arms, primary outcome.
	time to viral-, 6.9% lower, relative time 0.93, p = 0.47, treatment mean 9.5 (±5.0) n=50, control mean 10.2 (±4.6) n=50, moderate/severe, favipiravir arms, primary outcome.
[Auld], 4/26/2020, retrospective, USA, North America, peer-reviewed, 14 authors.	**risk of death, 2.8% higher, RR 1.03, p = 1.00**, treatment 33 of 114 (28.9%), control 29 of 103 (28.2%).
[Awad], 2/18/2021, retrospective, USA, North America, peer-reviewed, 4 authors, excluded in exclusion analyses: substantial confounding by time likely due to declining	**risk of death, 19.1% higher, RR 1.19, p = 0.60**, treatment 56 of 188 (29.8%), control 37 of 148 (25.0%).

usage over the early stages of the pandemic when overall treatment protocols improved dramatically, substantial unadjusted confounding by indication likely.	risk of mechanical ventilation, 460.7% higher, RR 5.61, $p < 0.001$, treatment 64 of 188 (34.0%), control 9 of 148 (6.1%), adjusted per study, odds ratio converted to relative risk.
	risk of ICU admission, 463.4% higher, RR 5.63, $p < 0.001$, treatment 67 of 188 (35.6%), control 9 of 148 (6.1%), adjusted per study, odds ratio converted to relative risk.
[Ayerbe], 9/30/2020, retrospective, database analysis, Spain, Europe, peer-reviewed, 3 authors.	**risk of death, 52.2% lower, RR 0.48, $p < 0.001$**, treatment 237 of 1,857 (12.8%), control 49 of 162 (30.2%), NNT 5.7, adjusted per study, odds ratio converted to relative risk.
[Azaña Gómez], 3/10/2022, retrospective, Spain, Europe, peer-reviewed, 10 authors, study period 1 March, 2020 - 1 October, 2020, excluded in exclusion analyses: unadjusted results with no group details.	**risk of death, 35.8% lower, RR 0.64, $p < 0.001$**, treatment 500 of 1,378 (36.3%), control 238 of 421 (56.5%), NNT 4.9.
[Babalola], 10/1/2021, Single Blind Randomized Controlled Trial, Nigeria, Africa, preprint, 6 authors, this trial uses multiple treatments in the treatment arm (combined with AZ) - results of individual treatments may vary.	**risk of no hospital discharge, 54.5% higher, RR 1.55, $p = 0.20$**, treatment 17 of 30 (56.7%), control 11 of 30 (36.7%), day 7.
	risk of no viral clearance, 9.5% lower, RR 0.90, $p = 0.78$, treatment 19 of 30 (63.3%), control 21 of 30 (70.0%), NNT 15, day 5 mid-recovery.
[Barbosa], 4/12/2020, retrospective, USA, North America, preprint, 5 authors, excluded in exclusion analyses: excessive unadjusted differences between groups.	**risk of death, 147.0% higher, RR 2.47, $p = 0.58$**, treatment 2 of 17 (11.8%), control 1 of 21 (4.8%).
[Barra], 7/31/2021, retrospective, Argentina, South America, preprint, 12 authors, average treatment delay 5.0 days, excluded in exclusion analyses: unadjusted results with no group details.	**risk of death, 10.8% lower, RR 0.89, $p = 1.00$**, treatment 2 of 18 (11.1%), control 81 of 650 (12.5%), NNT 74, unadjusted.
[Barrat-Due], 7/13/2021, Double Blind Randomized Controlled Trial, Norway, Europe, peer-reviewed, 41 authors, average treatment delay 8.0 days, trial NCT04321616.	**risk of death, 120.0% higher, RR 2.20, $p = 0.35$**, treatment 4 of 45 (8.9%), control 2 of 48 (4.2%), adjusted per study.
[Barry], 3/23/2021, retrospective, Saudi Arabia, Middle East, peer-reviewed, 14 authors.	**risk of death, 98.9% lower, RR 0.01, $p = 0.60$**, treatment 0 of 6 (0.0%), control 91 of 599 (15.2%), NNT 6.6, relative risk is not 0 because of continuity

	correction due to zero events (with reciprocal of the contrasting arm).
[Beaumont], 2/13/2022, retrospective, France, Europe, peer-reviewed, 22 authors, average treatment delay 6.0 days.	**risk of death/intubation, 14.1% lower, HR 0.86, p = 0.55**, treatment 7 of 38 (18.4%), control 88 of 258 (34.1%), NNT 6.4, adjusted per study, odds ratio converted to relative risk, Cox proportional hazards.
[Beltran Gonzalez], 2/23/2021, Double Blind Randomized Controlled Trial, Mexico, North America, peer-reviewed, mean age 53.8, 13 authors, average treatment delay 7.0 days, trial NCT04391127.	**risk of death, 62.6% lower, RR 0.37, p = 0.27**, treatment 2 of 33 (6.1%), control 6 of 37 (16.2%), NNT 9.8.
	risk of respiratory deterioration or death, 25.3% lower, RR 0.75, p = 0.57, treatment 6 of 33 (18.2%), control 9 of 37 (24.3%), NNT 16.
	risk of no hospital discharge, 12.1% higher, RR 1.12, p = 1.00, treatment 3 of 33 (9.1%), control 3 of 37 (8.1%).
[Berenguer], 8/3/2020, retrospective, Spain, Europe, peer-reviewed, 8 authors, average treatment delay 7.0 days.	**risk of death, 18.2% lower, RR 0.82, p < 0.001**, treatment 681 of 2,618 (26.0%), control 438 of 1,377 (31.8%), NNT 17.
[Bernaola], 7/21/2020, retrospective, Spain, Europe, preprint, 7 authors.	**risk of death, 17.0% lower, HR 0.83, p < 0.001**, treatment 236 of 1,498 (15.8%), control 28 of 147 (19.0%), NNT 30.
[Bielza], 12/11/2020, retrospective, Spain, Europe, peer-reviewed, median age 87.0, 24 authors, excluded in exclusion analyses: unadjusted results with no group details.	**risk of death, 21.5% lower, RR 0.78, p = 0.09**, treatment 33 of 91 (36.3%), control 249 of 539 (46.2%), NNT 10.
[Boari], 11/17/2020, retrospective, Italy, Europe, peer-reviewed, 20 authors, excluded in exclusion analyses: unadjusted results with no group details.	**risk of death, 54.5% lower, RR 0.45, p < 0.001**, treatment 41 of 202 (20.3%), control 25 of 56 (44.6%), NNT 4.1.
[Bosaeed], 4/30/2021, Randomized Controlled Trial, Saudi Arabia, Middle East, peer-reviewed, 30 authors, average treatment delay 5.85 days, excluded in exclusion analyses: very late stage, >50% on oxygen/ventilation at baseline.	**risk of death, 3.7% lower, RR 0.96, p = 0.91**, treatment 14 of 125 (11.2%), control 15 of 129 (11.6%), NNT 234, 90 days.
	risk of death, 28.6% lower, RR 0.71, p = 0.45, treatment 9 of 125 (7.2%), control 13 of 129 (10.1%), NNT 35, 28 days.
	risk of death, 65.1% higher, RR 1.65, p = 0.68, treatment 8 of 125 (6.4%), control 5 of 129 (3.9%), 14 days.

	risk of mechanical ventilation, 8.4% higher, RR 1.08, *p* = 0.78, treatment 21 of 125 (16.8%), control 20 of 129 (15.5%).
	risk of ICU admission, 31.0% higher, RR 1.31, *p* = 0.24, treatment 33 of 125 (26.4%), control 26 of 129 (20.2%).
	recovery time, 28.6% higher, relative time 1.29, *p* = 0.29, treatment 125, control 129.
	hospitalization time, 12.5% higher, relative time 1.12, *p* = 0.42, treatment 125, control 129.
	risk of no viral clearance, 2.6% lower, RR 0.97, *p* = 0.75, treatment 100 of 125 (80.0%), control 106 of 129 (82.2%), NNT 46.
[Bousquet], 6/23/2020, prospective, France, Europe, peer-reviewed, 10 authors.	**risk of death, 42.8% lower, RR 0.57, *p* = 0.15**, treatment 5 of 27 (18.5%), control 23 of 81 (28.4%), NNT 10, adjusted per study, odds ratio converted to relative risk.
[Budhiraja], 11/18/2020, retrospective, India, South Asia, preprint, 12 authors, excluded in exclusion analyses: excessive unadjusted differences between groups.	**risk of death, 65.4% lower, RR 0.35, *p* < 0.001**, treatment 69 of 834 (8.3%), control 34 of 142 (23.9%), NNT 6.4.
[Burdick], 11/26/2020, prospective, USA, North America, peer-reviewed, 14 authors.	**risk of death, 59.0% higher, HR 1.59, *p* = 0.12**, treatment 142, control 148, adjusted per study, all patients.
	risk of death, 71.0% lower, HR 0.29, *p* = 0.01, treatment 26, control 17, adjusted per study, subgroup of patients where treatment is predicted to be beneficial.
[Byakika-Kibwika], 6/4/2021, Randomized Controlled Trial, Uganda, Africa, preprint, 17 authors.	**recovery time, no change, relative time 1.00, *p* = 0.91**, treatment 36, control 29.
	relative improvement in Ct value, 29.3% better, RR 0.71, *p* = 0.47, treatment 15, control 15.
	risk of no viral clearance, 2.6% higher, RR 1.03, *p* = 1.00, treatment 35 of 55 (63.6%), control 31 of 50 (62.0%), day 6.
	risk of no viral clearance, 6.7% higher, RR 1.07, *p* = 0.85, treatment 27 of 55 (49.1%), control 23 of 50

	(46.0%), day 10.
[Calderón], 11/23/2021, retrospective, Mexico, North America, peer-reviewed, 7 authors, dosage 200mg bid days 1-7.	**risk of death, 214.8% higher, RR 3.15, *p* = 0.38**, treatment 5 of 27 (18.5%), control 1 of 17 (5.9%).
	risk of mechanical ventilation, 651.9% higher, RR 7.52, *p* = 0.15, treatment 4 of 27 (14.8%), control 0 of 17 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm).
	risk of ICU admission, 145.5% higher, RR 2.45, *p* < 0.001, treatment 16 of 27 (59.3%), control 0 of 17 (0.0%), adjusted per study.
	hospitalization time, 107.4% higher, relative time 2.07, *p* = 0.006, treatment 27, control 17.
[Cangiano], 12/22/2020, retrospective, Italy, Europe, peer-reviewed, 14 authors.	**risk of death, 73.4% lower, RR 0.27, *p* = 0.03**, treatment 5 of 33 (15.2%), control 37 of 65 (56.9%), NNT 2.4.
[Capsoni], 12/1/2020, retrospective, Italy, Europe, preprint, 13 authors, average treatment delay 7.0 days.	**risk of mechanical ventilation, 40.0% lower, RR 0.60, *p* = 0.30**, treatment 12 of 40 (30.0%), control 6 of 12 (50.0%), NNT 5.0.
[Catteau], 8/24/2020, retrospective, database analysis, Belgium, Europe, peer-reviewed, 11 authors, average treatment delay 5.0 days.	**risk of death, 32.0% lower, HR 0.68, *p* < 0.001**, treatment 804 of 4,542 (17.7%), control 957 of 3,533 (27.1%), NNT 11.
[Cavalcanti], 7/23/2020, Randomized Controlled Trial, Brazil, South America, peer-reviewed, baseline oxygen required 41.8%, 14 authors, average treatment delay 7.0 days.	**risk of death, 16.0% lower, RR 0.84, *p* = 0.77**, treatment 8 of 331 (2.4%), control 5 of 173 (2.9%), NNT 211, HCQ+HCQ/AZ.
	risk of hospitalization, 28.0% higher, RR 1.28, *p* = 0.30, treatment 331, control 173, HCQ+HCQ/AZ.
[Chari], 12/24/2020, retrospective, multiple countries, multiple regions, peer-reviewed, median age 69.0, 25 authors, excluded in exclusion analyses: unadjusted results with no group details.	**risk of death, 33.1% lower, RR 0.67, *p* = 0.17**, treatment 8 of 29 (27.6%), control 195 of 473 (41.2%), NNT 7.3.
[Chen (B)], 7/10/2020, Randomized Controlled Trial, Taiwan, Asia, peer-reviewed, 19 authors.	**risk of no viral clearance, 24.0% lower, RR 0.76, *p* = 0.71**, treatment 4 of 21 (19.0%), control 3 of 12 (25.0%), NNT 17, day 14.
	median time to PCR-, 50.0% lower, relative time 0.50, *p* = 0.40, treatment 21, control 12.

[Chen (C)], 7/10/2020, retrospective, Taiwan, Asia, peer-reviewed, 19 authors.	**risk of no viral clearance, 29.0% higher, RR 1.29, p = 0.70**, treatment 16 of 28 (57.1%), control 4 of 9 (44.4%), day 14.
[Chen (D)], 3/31/2020, Randomized Controlled Trial, China, Asia, preprint, 9 authors.	**risk of no improvement in pneumonia at day 6, 57.0% lower, RR 0.43, p = 0.04**, treatment 6 of 31 (19.4%), control 14 of 31 (45.2%), NNT 3.9.
[Chen (E)], 3/6/2020, Randomized Controlled Trial, China, Asia, peer-reviewed, 14 authors.	**risk of radiological progression, 29.0% lower, RR 0.71, p = 0.57**, treatment 5 of 15 (33.3%), control 7 of 15 (46.7%), NNT 7.5.
	risk of viral+ at day 7, 100% higher, RR 2.00, p = 1.00, treatment 2 of 15 (13.3%), control 1 of 15 (6.7%).
[Choi], 10/27/2020, retrospective, database analysis, South Korea, Asia, peer-reviewed, 8 authors, excluded in exclusion analyses: excessive unadjusted differences between groups.	**median time to PCR-, 22.0% higher, relative time 1.22, p < 0.001**, treatment 701, control 701.
[Coll], 10/23/2020, retrospective, Spain, Europe, peer-reviewed, median age 61.0, 29 authors, excluded in exclusion analyses: unadjusted results with no group details.	**risk of death, 45.6% lower, RR 0.54, p < 0.001**, treatment 55 of 307 (17.9%), control 108 of 328 (32.9%), NNT 6.7.
[Corradini], 4/24/2021, retrospective, Italy, Europe, peer-reviewed, 60 authors, dosage not specified.	**risk of death, 70.2% lower, OR 0.30, p < 0.001**, treatment 1,439, control 274, adjusted per study, Table S6, all patients, multivariable, RR approximated with OR.
	risk of death, 76.8% lower, OR 0.23, p < 0.001, treatment 546, control 71, adjusted per study, Table S6, mild condition patients, multivariable, RR approximated with OR.
	risk of death, 84.2% lower, OR 0.16, p < 0.001, treatment 184, control 64, adjusted per study, Table S6, moderate condition patients, multivariable, RR approximated with OR.
	risk of death, 29.0% higher, OR 1.29, p = 0.73, treatment 68, control 37, adjusted per study, Table S6, severe condition patients, multivariable, RR approximated with OR.
[Cortez], 11/11/2021, retrospective, Philippines, Asia, peer-reviewed, 29 authors, study period March 2020 -	**risk of death, 15.0% lower, RR 0.85, p = 1.00**, treatment 1 of 25 (4.0%), control 12 of 255 (4.7%), NNT 142.

October 2020, excluded in exclusion analyses: unadjusted results with no group details.	
[Cravedi], 7/10/2020, retrospective, USA, North America, peer-reviewed, mean age 60.0, 25 authors, average treatment delay 6.0 days, excluded in exclusion analyses: substantial unadjusted confounding by indication likely.	risk of death, 53.0% higher, RR 1.53, $p = 0.17$, treatment 36 of 101 (35.6%), control 10 of 43 (23.3%).
[D'Arminio Monforte], 7/29/2020, retrospective, Italy, Europe, preprint, 5 authors.	risk of death, 34.0% lower, HR 0.66, $p = 0.12$, treatment 53 of 197 (26.9%), control 47 of 92 (51.1%), NNT 4.1, adjusted per study.
[Davido], 8/2/2020, retrospective, France, Europe, peer-reviewed, 14 authors.	risk of intubation/hospitalization, 55.0% lower, HR 0.45, $p = 0.04$, treatment 12 of 80 (15.0%), control 13 of 40 (32.5%), NNT 5.7.
[De Luna], 12/14/2020, retrospective, Dominican Republic, Caribbean, preprint, 10 authors, excluded in exclusion analyses: unadjusted results with no group details, substantial unadjusted confounding by indication likely.	risk of death, 104.5% higher, RR 2.05, $p = 0.69$, treatment 15 of 132 (11.4%), control 1 of 18 (5.6%).
[De Rosa], 5/1/2021, retrospective, Italy, Europe, peer-reviewed, 20 authors, average treatment delay 6.0 days.	risk of death, 35.0% lower, RR 0.65, $p = 0.02$, treatment 118 of 731 (16.1%), control 80 of 280 (28.6%), NNT 8.0, adjusted per study, odds ratio converted to relative risk, multivariate logistic regression, patients alive at day 7.
[Di Castelnuovo], 1/29/2021, retrospective, Italy, Europe, peer-reviewed, 112 authors.	risk of death, 40.0% lower, RR 0.60, $p < 0.001$, treatment 3,270, control 1,000, odds ratio converted to relative risk, multivariate Cox proportional hazards model 4, control prevalence approximated with overall prevalence.
[Di Castelnuovo (B)], 8/25/2020, retrospective, Italy, Europe, peer-reviewed, 110 authors.	risk of death, 30.0% lower, HR 0.70, $p < 0.001$, treatment 386 of 2,634 (14.7%), control 90 of 817 (11.0%), adjusted per study.
[Dubee], 10/21/2020, Randomized Controlled Trial, France, Europe, peer-reviewed, median age 77.0, 18 authors, average treatment delay 5.0 days, trial NCT04325893.	risk of death at day 28, 46.0% lower, RR 0.54, $p = 0.21$, treatment 6 of 124 (4.8%), control 11 of 123 (8.9%), NNT 24.
	risk of combined intubation/death at day 28, 26.0% lower, RR 0.74, $p = 0.48$, treatment 9 of 124 (7.3%), control 12 of 123 (9.8%), NNT 40.

[Dubernet], 8/20/2020, retrospective, France, Europe, peer-reviewed, median age 66.0, 20 authors.	**risk of ICU admission, 87.6% lower, RR 0.12, *p* = 0.008**, treatment 1 of 17 (5.9%), control 9 of 19 (47.4%), NNT 2.4.
[Ebongue], 3/18/2022, retrospective, Cameroon, Africa, peer-reviewed, 27 authors, this trial uses multiple treatments in the treatment arm (combined with AZ) - results of individual treatments may vary.	**risk of death, 43.0% lower, HR 0.57, *p* = 0.04**, treatment 93 of 522 (17.8%), control 36 of 58 (62.1%), NNT 2.3, adjusted per study, multivariable.
[Falcone], 11/19/2020, prospective, propensity score matching, Italy, Europe, peer-reviewed, 19 authors, average treatment delay 6.5 days.	**risk of death, 65.0% lower, RR 0.35, *p* = 0.20**, treatment 40 of 238 (16.8%), control 30 of 77 (39.0%), NNT 4.5, adjusted per study, PSM.
	risk of death, 25.0% lower, RR 0.75, *p* = 0.36, treatment 40 of 238 (16.8%), control 30 of 77 (39.0%), NNT 4.5, adjusted per study, multivariate Cox regression.
	risk of death, 57.0% lower, RR 0.43, *p* < 0.001, treatment 40 of 238 (16.8%), control 30 of 77 (39.0%), NNT 4.5, adjusted per study, univariate Cox regression.
[Faíco-Filho], 6/21/2020, prospective, Brazil, South America, peer-reviewed, median age 58.0, 6 authors.	**Δt7-12 ΔCt improvement, 80.8% lower, relative rate 0.19, *p* = 0.40**, treatment 34, control 32.
	Δt<7 ΔCt improvement, 24.0% lower, relative rate 0.76, *p* = 0.36, treatment 34, control 32.
	Δt>12 ΔCt improvement, 15.0% higher, relative rate 1.15, *p* = 0.52, treatment 34, control 32.
[Ferreira], 11/26/2021, retrospective, Brazil, South America, peer-reviewed, 5 authors, study period 12 March, 2020 - 8 July, 2020, average treatment delay 7.0 days, dosage not specified.	**risk of death, 151.5% higher, RR 2.51, *p* = 0.03**, treatment 17 of 111 (15.3%), control 11 of 81 (13.6%), odds ratio converted to relative risk, multivariate.
	risk of death/intubation, 45.9% higher, RR 1.46, *p* = 0.23, treatment 30 of 111 (27.0%), control 15 of 81 (18.5%).
	risk of death/intubation/ICU, 61.3% higher, RR 1.61, *p* = 0.04, treatment 42 of 111 (37.8%), control 19 of 81 (23.5%).
[Fontana], 6/22/2020, retrospective, Italy, Europe, peer-reviewed, 8 authors.	**risk of death, 50.0% lower, RR 0.50, *p* = 0.53**, treatment 4 of 12 (33.3%), control 2 of 3 (66.7%), NNT 3.0.

[Fried], 8/28/2020, retrospective, database analysis, USA, North America, peer-reviewed, 11 authors, excluded in exclusion analyses: excessive unadjusted differences between groups, substantial unadjusted confounding by indication likely.	**risk of death, 27.0% higher, RR 1.27, $p < 0.001$**, treatment 1,048 of 4,232 (24.8%), control 1,466 of 7,489 (19.6%).
[Frontera], 10/26/2020, retrospective, propensity score matching, USA, North America, preprint, median age 64.0, 14 authors, this trial uses multiple treatments in the treatment arm (combined with zinc) - results of individual treatments may vary.	**risk of death, 37.0% lower, HR 0.63, $p = 0.01$**, treatment 121 of 1,006 (12.0%), control 424 of 2,467 (17.2%), NNT 19, adjusted per study, PSM.
	risk of death, 24.0% lower, HR 0.76, $p = 0.02$, treatment 121 of 1,006 (12.0%), control 424 of 2,467 (17.2%), NNT 19, adjusted per study, regression.
[Gadhiya], 4/8/2021, retrospective, USA, North America, peer-reviewed, 4 authors, excluded in exclusion analyses: substantial confounding by time likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically, substantial unadjusted confounding by indication likely.	**risk of death, 4.8% higher, RR 1.05, $p = 0.89$**, treatment 22 of 55 (40.0%), control 33 of 216 (15.3%), adjusted per study, odds ratio converted to relative risk, multivariate logistic regression.
[Geleris], 5/7/2020, retrospective, USA, North America, peer-reviewed, 12 authors, excluded in exclusion analyses: significant issues found with adjustments.	**risk of death/intubation, 4.0% higher, HR 1.04, $p = 0.76$**, treatment 262 of 811 (32.3%), control 84 of 565 (14.9%), adjusted per study.
[Gerlovin], 6/24/2021, retrospective, USA, North America, peer-reviewed, 21 authors.	**risk of death, 22.0% higher, HR 1.22, $p = 0.18$**, treatment 90 of 429 (21.0%), control 141 of 770 (18.3%), adjusted per study, HCQ+AZ.
	risk of death, 21.0% higher, HR 1.21, $p = 0.33$, treatment 49 of 228 (21.5%), control 141 of 770 (18.3%), adjusted per study, HCQ.
	risk of mechanical ventilation, 55.0% higher, HR 1.55, $p = 0.02$, treatment 64 of 429 (14.9%), control 69 of 770 (9.0%), adjusted per study, HCQ+AZ.
	risk of mechanical ventilation, 33.0% higher, HR 1.33, $p = 0.25$, treatment 32 of 228 (14.0%), control 69 of 770 (9.0%), adjusted per study, HCQ.
[Goldman], 5/27/2020, retrospective, multiple countries, multiple regions, peer-reviewed, 26 authors, excluded in exclusion	**risk of death, 22.3% lower, RR 0.78, $p = 0.46$**, treatment 10 of 109 (9.2%), control 34 of 288 (11.8%), NNT 38.

analyses: unadjusted results with no group details.	
[Gonzalez], 8/21/2020, retrospective, database analysis, Spain, Europe, preprint, 25 authors.	risk of death, 26.6% lower, RR 0.73, p = 0.06, treatment 1,246 of 8,476 (14.7%), control 341 of 1,168 (29.2%), NNT 6.9, adjusted per study, odds ratio converted to relative risk.
[Guglielmetti], 10/25/2021, retrospective, Italy, Europe, peer-reviewed, 19 authors, study period 21 February, 2020 - 15 May, 2020.	risk of death, 28.0% lower, HR 0.72, p = 0.10, treatment 474, control 126, multivariable Cox proportional hazards.
[Guglielmetti (B)], 12/9/2020, retrospective, Italy, Europe, peer-reviewed, 16 authors, average treatment delay 8.0 days.	risk of death, 35.0% lower, RR 0.65, p = 0.22, treatment 181, control 37, adjusted per study, multivariable Cox.
[Guisado-Vasco (B)], 10/15/2020, retrospective, Spain, Europe, peer-reviewed, median age 69.0, 25 authors.	risk of death, 20.3% lower, RR 0.80, p = 0.36, treatment 127 of 558 (22.8%), control 14 of 49 (28.6%), NNT 17, adjusted per study, odds ratio converted to relative risk.
[Gupta], 7/15/2020, retrospective, USA, North America, peer-reviewed, baseline oxygen required 87.1%, 34 authors, excluded in exclusion analyses: very late stage, >50% on oxygen/ventilation at baseline.	risk of death, 6.0% higher, RR 1.06, p = 0.41, treatment 631 of 1,761 (35.8%), control 153 of 454 (33.7%).
[Güner], 12/29/2020, retrospective, Turkey, Europe, peer-reviewed, 23 authors.	risk of ICU admission, 77.3% lower, RR 0.23, p = 0.16, treatment 604, control 100, IPTW multivariate analysis, HCQ vs. favipiravir.
[Hafez], 4/8/2022, retrospective, United Arab Emirates, Middle East, peer-reviewed, 6 authors.	viral clearance time, 12.3% lower, HR 0.88, p = 0.59, treatment 40, control 1,446, Cox proportional hazards.
	viral clearance time, 58.7% lower, HR 0.41, p = 0.09, treatment 4, control 1,446, HCQ + favipiravir + lopinavir/ritonavir, Cox proportional hazards.
[Haji Aghajani], 4/29/2021, retrospective, Iran, Middle East, peer-reviewed, 7 authors.	risk of death, 19.5% lower, HR 0.81, p = 0.09, treatment 553, control 438, adjusted per study, Cox proportional hazards, RR approximated with OR.
[Hall], 2/18/2022, retrospective, USA, North America, peer-reviewed, 15 authors, excluded in exclusion analyses: unadjusted results with no group details.	risk of death, 11.2% lower, RR 0.89, p = 0.31, treatment 31 of 56 (55.4%), control 280 of 449 (62.4%), NNT 14.

[Heberto], 9/12/2020, prospective, Mexico, North America, peer-reviewed, 8 authors, this trial uses multiple treatments in the treatment arm (combined with AZ) - results of individual treatments may vary.	**risk of death, 53.9% lower, RR 0.46, p = 0.04**, treatment 139, control 115, odds ratio converted to relative risk.
	risk of mechanical ventilation, 65.1% lower, RR 0.35, p = 0.008, treatment 139, control 115, odds ratio converted to relative risk.
[Hernandez-Cardenas], 2/5/2021, Randomized Controlled Trial, Mexico, North America, preprint, 6 authors, average treatment delay 7.4 days.	**risk of death, 12.0% lower, RR 0.88, p = 0.66**, treatment 106, control 108.
	risk of death, 57.0% lower, RR 0.43, p = 0.29, subgroup not intubated at baseline.
[Hong (B)], 5/4/2022, retrospective, South Korea, Asia, peer-reviewed, 11 authors, study period 28 February, 2020 - 28 April, 2020.	**recovery time, 24.9% lower, HR 0.75, p = 0.45**, treatment 15, control 15, propensity score matching.
	hospitalization time, 12.7% higher, HR 1.13, p = 0.75, treatment 15, control 15, propensity score matching.
	viral clearance time, 0.5% lower, HR 1.00, p = 0.99, treatment 15, control 15, propensity score matching.
[Hraiech], 5/24/2020, retrospective, France, Europe, peer-reviewed, 8 authors, average treatment delay 7.0 days, excluded in exclusion analyses: very late stage, ICU patients.	**risk of death, 64.7% lower, RR 0.35, p = 0.21**, treatment 2 of 17 (11.8%), control 5 of 15 (33.3%), NNT 4.6, day 38 +- 7.
	risk of death, 376.5% higher, RR 4.76, p = 0.49, treatment 2 of 17 (11.8%), control 0 of 15 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm), day 6 from ARDS.
	risk of no viral clearance, 2.9% higher, RR 1.03, p = 1.00, treatment 14 of 17 (82.4%), control 8 of 10 (80.0%), day 6 from treatment.
[Huang (D)], 5/28/2020, prospective, China, Asia, peer-reviewed, 36 authors.	**time to viral-, 67.0% lower, relative time 0.33, p < 0.001**, treatment 197, control 176.
	time to viral-, 59.1% lower, relative time 0.41, p < 0.001, treatment 32, control 37, early treatment.
[Ip (B)], 5/25/2020, retrospective, database analysis, USA, North America, peer-reviewed, 32 authors, average treatment delay 5.0 days.	**risk of death, 1.0% lower, HR 0.99, p = 0.93**, treatment 432 of 1,914 (22.6%), control 115 of 598 (19.2%), adjusted per study.
[Izoulet], 4/21/2020, retrospective, multiple countries, multiple regions, preprint, 1	**risk of death, 85.0% lower, RR 0.15, p < 0.001**.

author, dosage not specified, excluded in exclusion analyses: excessive unadjusted differences between groups.	
[Jacobs], 7/6/2021, prospective, USA, North America, peer-reviewed, 14 authors, excluded in exclusion analyses: unadjusted results with no group details, substantial confounding by time likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically.	**risk of death, 6.6% lower, RR 0.93, *p* = 0.74**, treatment 24 of 46 (52.2%), control 86 of 154 (55.8%), NNT 27.
[Johnston], 12/9/2020, Randomized Controlled Trial, USA, North America, peer-reviewed, 30 authors, average treatment delay 5.9 days, dosage 400mg bid day 1, 200mg bid days 2-10, trial NCT04354428.	**risk of hospitalization, 29.9% lower, RR 0.70, *p* = 0.73**, treatment 5 of 148 (3.4%), control 4 of 83 (4.8%), NNT 69, HCQ + folic acid and HCQ + AZ vs. vitamin C + folic acid.
	risk of no recovery, 2.0% lower, RR 0.98, *p* = 0.95, treatment 30 of 60 (50.0%), control 34 of 72 (47.2%), adjusted per study, HCQ + folic acid vs. vitamin C + folic acid.
	risk of no recovery, 9.9% higher, RR 1.10, *p* = 0.70, treatment 34 of 65 (52.3%), control 34 of 72 (47.2%), adjusted per study, HCQ + AZ vs. vitamin C + folic acid.
	risk of no viral clearance, 38.3% lower, RR 0.62, *p* = 0.047, treatment 6 of 49 (12.2%), control 12 of 52 (23.1%), NNT 9.2, adjusted per study, HCQ + folic acid vs. vitamin C + folic acid.
	risk of no viral clearance, 20.0% lower, RR 0.80, *p* = 0.49, treatment 11 of 51 (21.6%), control 12 of 52 (23.1%), adjusted per study, HCQ + AZ vs. vitamin C + folic acid.
[Kalligeros], 8/5/2020, retrospective, USA, North America, peer-reviewed, 13 authors, average treatment delay 6.0 days.	**risk of death, 67.0% higher, HR 1.67, *p* = 0.57**, treatment 36, control 72.
[Kamran], 8/4/2020, prospective, Pakistan, South Asia, preprint, 10 authors, excluded in exclusion analyses: excessive unadjusted differences between groups.	**risk of progression, 5.0% lower, RR 0.95, *p* = 1.00**, treatment 11 of 349 (3.2%), control 5 of 151 (3.3%), NNT 627.
	risk of progression, 54.8% lower, RR 0.45, *p* = 0.30, treatment 4 of 31 (12.9%), control 2 of 7 (28.6%), NNT 6.4, with comorbidities.

	risk of viral+ at day 14, 10.0% higher, RR 1.10, *p* = 0.52, treatment 349, control 151.
[Karruli], 9/1/2021, retrospective, Italy, Europe, peer-reviewed, 13 authors, study period March 2020 - May 2020, excluded in exclusion analyses: unadjusted results with no group details.	**risk of death, 4.8% lower, RR 0.95, *p* = 1.00**, treatment 20 of 28 (71.4%), control 3 of 4 (75.0%), NNT 28.
[Kelly], 7/22/2020, retrospective, Ireland, Europe, peer-reviewed, 14 authors, excluded in exclusion analyses: substantial unadjusted confounding by indication likely.	**risk of death, 143.0% higher, RR 2.43, *p* = 0.03**, treatment 23 of 82 (28.0%), control 6 of 52 (11.5%).
[Kim], 5/18/2020, retrospective, South Korea, Asia, preprint, 11 authors.	**hospitalization time, 51.0% lower, relative time 0.49, *p* = 0.01**, treatment 22, control 40.
	time to viral-, 56.0% lower, relative time 0.44, *p* = 0.005, treatment 22, control 40.
[Kokturk], 4/28/2021, retrospective, database analysis, Turkey, Europe, peer-reviewed, 68 authors.	**risk of death, 3.8% higher, RR 1.04, *p* = 0.97**, treatment 62 of 1,382 (4.5%), control 5 of 118 (4.2%), adjusted per study, odds ratio converted to relative risk.
[Komissarov], 6/30/2020, retrospective, Russia, Europe, preprint, 8 authors.	**risk of viral load, 25.0% higher, RR 1.25, *p* = 0.45**, treatment 26, control 10.
[Krishnan], 7/20/2020, retrospective, USA, North America, peer-reviewed, 13 authors, dosage not specified, excluded in exclusion analyses: unadjusted results with no group details.	**risk of death, 20.4% lower, RR 0.80, *p* = 0.48**, treatment 86 of 144 (59.7%), control 6 of 8 (75.0%), NNT 6.5.
[Kuderer], 5/28/2020, retrospective, USA, North America, peer-reviewed, 73 authors, excluded in exclusion analyses: substantial unadjusted confounding by indication likely.	**risk of death, 134.2% higher, RR 2.34, *p* < 0.001**, treatment 45 of 181 (24.9%), control 121 of 928 (13.0%), odds ratio converted to relative risk, HCQ+AZ.
[Lagier], 6/4/2021, retrospective, France, Europe, peer-reviewed, 32 authors.	**risk of death, 32.0% lower, HR 0.68, *p* = 0.004**, treatment 93 of 1,270 (7.3%), control 146 of 841 (17.4%), NNT 10.0, adjusted per study, multivariable, Cox proportional hazards.
[Lagier (B)], 6/25/2020, retrospective, France, Europe, peer-reviewed, 22 authors, dosage 200mg tid days 1-10.	**risk of death, 59.0% lower, HR 0.41, *p* = 0.048**, treatment 35 of 3,119 (1.1%), control 58 of 618 (9.4%), adjusted per study.

[Lamback], 2/19/2021, retrospective, Brazil, South America, peer-reviewed, 10 authors, excluded in exclusion analyses: substantial confounding by time likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically.	**risk of death, 8.9% lower, RR 0.91, *p* = 0.83**, treatment 11 of 101 (10.9%), control 11 of 92 (12.0%), NNT 94.
	risk of ICU admission, 19.9% higher, RR 1.20, *p* = 0.61, treatment 25 of 101 (24.8%), control 19 of 92 (20.7%).
[Lambermont], 11/28/2020, retrospective, Belgium, Europe, peer-reviewed, 15 authors.	**risk of death, 32.3% lower, RR 0.68, *p* = 0.46**, treatment 97 of 225 (43.1%), control 14 of 22 (63.6%), NNT 4.9, adjusted per study.
[Lammers], 9/29/2020, prospective, Netherlands, Europe, peer-reviewed, 18 authors.	**risk of death/ICU, 32.0% lower, HR 0.68, *p* = 0.02**, treatment 30 of 189 (15.9%), control 101 of 498 (20.3%), adjusted per study.
[Lano], 10/21/2020, retrospective, France, Europe, peer-reviewed, median age 73.5, 30 authors.	**risk of death, 33.1% lower, RR 0.67, *p* = 0.28**, treatment 56, control 66, adjusted per study, odds ratio converted to relative risk.
	risk of death/ICU, 38.9% lower, RR 0.61, *p* = 0.23, treatment 17 of 56 (30.4%), control 28 of 66 (42.4%), NNT 8.3, adjusted per study, odds ratio converted to relative risk.
	risk of death/ICU, 68.7% lower, RR 0.31, *p* = 0.11, treatment 4 of 36 (11.1%), control 11 of 31 (35.5%), NNT 4.1, not requiring O2 on diagnosis (relatively early treatment).
[Lauriola], 9/14/2020, retrospective, Italy, Europe, peer-reviewed, mean age 71.8, 10 authors.	**risk of death, 73.5% lower, HR 0.27, *p* < 0.001**, treatment 102 of 297 (34.3%), control 35 of 63 (55.6%), NNT 4.7, adjusted per study.
[Lavilla Olleros], 1/21/2022, retrospective, Spain, Europe, peer-reviewed, 22 authors.	**risk of death, 36.2% lower, RR 0.64, *p* < 0.001**, treatment 2,285 of 12,772 (17.9%), control 774 of 2,149 (36.0%), NNT 5.5, adjusted per study, odds ratio converted to relative risk, multivariable.
[Lecronier], 7/11/2020, retrospective, France, Europe, peer-reviewed, baseline oxygen required 100.0%, 25 authors, HCQ vs. control, excluded in exclusion analyses: very late stage, >50% on oxygen/ventilation at baseline.	**risk of death, 42.0% lower, RR 0.58, *p* = 0.24**, treatment 9 of 38 (23.7%), control 9 of 22 (40.9%), NNT 5.8.
	risk of treatment escalation, 6.0% lower, RR 0.94, *p* = 0.73, treatment 15 of 38 (39.5%), control 9 of 22 (40.9%), NNT 70.
	risk of viral+ at day 7, 15.0% lower, RR 0.85, *p* = 0.61, treatment 19 of 26 (73.1%), control 12 of 14 (85.7%),

	NNT 7.9.
[Li], 1/18/2021, retrospective, China, Asia, peer-reviewed, 21 authors.	**risk of no hospital discharge, 50.0% lower, HR 0.50, p = 0.09**, treatment 14, control 14, RCT patients vs. matched sample of non-treated patients.
[Li (B)], 1/12/2021, retrospective, database analysis, China, Asia, preprint, 5 authors.	**time to viral-, 40.0% higher, relative time 1.40, p = 0.06**, treatment 18, control 19.
[Lora-Tamayo], 2/11/2021, retrospective, Spain, Europe, peer-reviewed, 10 authors.	**risk of death, 50.5% lower, RR 0.50, p < 0.001**, treatment 7,192, control 1,361, odds ratio converted to relative risk, univariate, control prevalence approximated with overall prevalence.
[Lotfy], 1/1/2021, retrospective, Saudi Arabia, Middle East, peer-reviewed, mean age 55.0, 3 authors, excluded in exclusion analyses: substantial confounding by time likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically, substantial unadjusted confounding by indication likely.	**risk of death, 24.8% higher, RR 1.25, p = 0.76**, treatment 6 of 99 (6.1%), control 5 of 103 (4.9%).
	risk of mechanical ventilation, 41.2% higher, RR 1.41, p = 0.34, treatment 19 of 99 (19.2%), control 14 of 103 (13.6%).
	risk of ICU admission, 16.5% higher, RR 1.17, p = 0.53, treatment 28 of 99 (28.3%), control 25 of 103 (24.3%).
[Luo], 6/17/2020, retrospective, USA, North America, peer-reviewed, 31 authors, excluded in exclusion analyses: substantial unadjusted confounding by indication likely.	**risk of death, 2.2% higher, RR 1.02, p = 0.99**, treatment 11 of 35 (31.4%), control 4 of 13 (30.8%), odds ratio converted to relative risk.
[Luo (B)], 5/21/2020, retrospective, China, Asia, peer-reviewed, 9 authors.	**risk of death, 32.4% lower, OR 0.68, p = 0.72**, treatment 19, control 264, multivariate, RR approximated with OR.
[Lyngbakken], 7/17/2020, Randomized Controlled Trial, Norway, Europe, peer-reviewed, median age 62.0, 11 authors, average treatment delay 8.0 days, trial NCT04316377.	**risk of death, 3.7% lower, RR 0.96, p = 1.00**, treatment 1 of 27 (3.7%), control 1 of 26 (3.8%), NNT 702.
	improvement in viral load reduction rate, 71.0% lower, relative rate 0.29, p = 0.51, treatment 27, control 26.
[López], 11/2/2020, retrospective, Spain, Europe, peer-reviewed, 7 authors.	**risk of progression, 64.3% lower, RR 0.36, p = 0.02**, treatment 5 of 36 (13.9%), control 14 of 36 (38.9%), NNT 4.0.
[Magagnoli], 4/21/2020, retrospective, database analysis, USA, North America, peer-reviewed, 7 authors.	**risk of death, 11.0% lower, HR 0.89, p = 0.74**, treatment 39 of 148 (26.4%), control 18 of 163 (11.0%), adjusted per study, HCQ+AZ w/dispositions.

	risk of death, 1.0% lower, HR 0.99, p = 0.98, treatment 30 of 114 (26.3%), control 18 of 163 (11.0%), adjusted per study, HCQ w/dispositions.
	risk of death, 31.0% higher, HR 1.31, p = 0.28, treatment 49 of 214 (22.9%), control 37 of 395 (9.4%), adjusted per study, HCQ+AZ.
	risk of death, 83.0% higher, HR 1.83, p = 0.009, treatment 38 of 198 (19.2%), control 37 of 395 (9.4%), adjusted per study, HCQ.
[Mahale], 12/31/2020, retrospective, India, South Asia, peer-reviewed, 22 authors, study period 22 March, 2020 - 21 May, 2020, excluded in exclusion analyses: unadjusted results with no group details.	risk of death, 28.7% lower, RR 0.71, p = 0.36, treatment 25 of 102 (24.5%), control 11 of 32 (34.4%), NNT 10.
[Mahévas], 5/14/2020, retrospective, France, Europe, peer-reviewed, 34 authors, average treatment delay 7.0 days.	risk of death, 20.0% higher, HR 1.20, p = 0.75, treatment 9 of 84 (10.7%), control 8 of 89 (9.0%), adjusted per study.
[Maldonado], 11/5/2020, retrospective, Spain, Europe, peer-reviewed, 10 authors, excluded in exclusion analyses: treatment or control group size extremely small.	risk of death, 90.9% lower, RR 0.09, p = 0.17, treatment 1 of 11 (9.1%), control 1 of 1 (100.0%), NNT 1.1.
[Mallat], 5/2/2020, retrospective, United Arab Emirates, Middle East, peer-reviewed, 8 authors, average treatment delay 4.0 days.	time to viral-, 203.0% higher, relative time 3.03, p = 0.02, treatment 23, control 11.
[Martin-Vicente], 3/8/2021, retrospective, Spain, Europe, preprint, 38 authors, excluded in exclusion analyses: unadjusted results with no group details, treatment or control group size extremely small.	risk of death, 59.3% lower, RR 0.41, p = 0.41, treatment 37 of 91 (40.7%), control 1 of 1 (100.0%), NNT 1.7.
[Martinez-Lopez], 6/30/2020, retrospective, Spain, Europe, peer-reviewed, median age 71.0, 25 authors.	risk of death, 33.0% lower, RR 0.67, p = 0.20, treatment 47 of 148 (31.8%), control 9 of 19 (47.4%), NNT 6.4.
[Matangila], 12/18/2020, retrospective, DR Congo, Africa, peer-reviewed, median age 54.0, 12 authors, average treatment delay 7.0 days.	risk of death, 54.9% lower, RR 0.45, p = 0.21, treatment 25 of 147 (17.0%), control 8 of 13 (61.5%), NNT 2.2, adjusted per study, odds ratio converted to relative risk.
[McGrail], 7/19/2020, retrospective, USA, North America, preprint, 2 authors,	risk of death, 70.0% higher, RR 1.70, p = 0.69, treatment 4 of 33 (12.1%), control 3 of 42 (7.1%).

excluded in exclusion analyses: excessive unadjusted differences between groups.	
[Membrillo de Novales], 5/5/2020, retrospective, Spain, Europe, preprint, 19 authors, average treatment delay 7.0 days.	risk of death, 55.1% lower, RR 0.45, p = 0.002, treatment 27 of 123 (22.0%), control 21 of 43 (48.8%), NNT 3.7.
[Menardi], 9/30/2021, retrospective, Italy, Europe, peer-reviewed, 10 authors, excluded in exclusion analyses: excessive unadjusted differences between groups, substantial unadjusted confounding by indication likely.	risk of death, 35.2% lower, RR 0.65, p = 0.12, treatment 32 of 200 (16.0%), control 19 of 77 (24.7%), NNT 12.
[Mikami], 6/30/2020, retrospective, USA, North America, peer-reviewed, 7 authors.	risk of death, 47.0% lower, HR 0.53, p < 0.001, treatment 575 of 2,077 (27.7%), control 231 of 743 (31.1%), adjusted per study.
[Modrák], 12/4/2020, retrospective, Czech Republic, Europe, preprint, 26 authors.	risk of death, 59.0% lower, RR 0.41, p = 0.04, treatment 108, control 105, Cox (single).
[Mohandas], 4/26/2021, retrospective, India, South Asia, peer-reviewed, 6 authors, excluded in exclusion analyses: substantial unadjusted confounding by indication likely, unadjusted results with no group details, substantial confounding by time likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically.	risk of death, 81.0% higher, RR 1.81, p = 0.007, treatment 27 of 384 (7.0%), control 115 of 2,961 (3.9%).
[Mulhem], 4/7/2021, retrospective, database analysis, USA, North America, peer-reviewed, 3 authors, excluded in exclusion analyses: substantial unadjusted confounding by indication likely, substantial confounding by time likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically.	risk of death, 28.3% higher, RR 1.28, p = 0.10, treatment 435 of 2,496 (17.4%), control 81 of 723 (11.2%), adjusted per study, odds ratio converted to relative risk, logistic regression.
[Nachega], 10/2/2020, retrospective, database analysis, DR Congo, Africa, peer-reviewed, median age 46.0, 25 authors.	risk of death, 27.6% lower, RR 0.72, p = 0.17, treatment 69 of 630 (11.0%), control 28 of 96 (29.2%), NNT 5.5, adjusted per study, odds ratio converted to relative risk.
	risk of no improvement, 25.8% better, RR 0.74, p = 0.13, adjusted per study, odds ratio converted to relative risk.

[Naseem], 12/14/2020, retrospective, Pakistan, South Asia, preprint, 5 authors.	**risk of death, 33.3% lower, RR 0.67, *p* = 0.34**, treatment 77, control 1,137, multivariate Cox.
[Niwas], 11/1/2020, retrospective, India, South Asia, peer-reviewed, mean age 45.5, 17 authors, excluded in exclusion analyses: excessive unadjusted differences between groups.	**recovery time, 29.2% lower, relative time 0.71, *p* = 0.008**, treatment mean 6.3 (±2.7) n=12, control mean 8.9 (±2.2) n=17.
	risk of no viral clearance, 183.3% higher, RR 2.83, *p* = 0.55, treatment 2 of 12 (16.7%), control 1 of 17 (5.9%).
[Núñez-Gil], 11/9/2020, retrospective, database analysis, multiple countries, multiple regions, peer-reviewed, median age 68.0, 49 authors.	**risk of death, 7.9% lower, RR 0.92, *p* = 0.005**, treatment 200 of 686 (29.2%), control 100 of 268 (37.3%), adjusted per study, odds ratio converted to relative risk.
[Omma], 1/31/2022, retrospective, Turkey, Europe, peer-reviewed, 11 authors, study period 1 April, 2020 - 31 December, 2020.	**risk of death, 28.2% lower, RR 0.72, *p* = 0.30**, treatment 17 of 213 (8.0%), control 20 of 180 (11.1%), NNT 32.
	risk of ICU admission, 50.2% lower, RR 0.50, *p* = 0.004, treatment 23 of 213 (10.8%), control 39 of 180 (21.7%), NNT 9.2.
	hospitalization time, 16.7% lower, relative time 0.83, *p* = 0.007, treatment 213, control 180.
[Orioli], 12/14/2020, retrospective, Belgium, Europe, peer-reviewed, 9 authors.	**risk of death, 12.7% lower, RR 0.87, *p* = 1.00**, treatment 8 of 55 (14.5%), control 3 of 18 (16.7%), NNT 47.
[Ouedraogo], 2/5/2021, retrospective, Burkina Faso, Africa, peer-reviewed, 14 authors.	**risk of death, 33.0% lower, HR 0.67, *p* = 0.38**, treatment 397, control 59, multivariate.
	risk of ARDS, 68.0% lower, OR 0.32, *p* = 0.001, treatment 397, control 59, multivariate, RR approximated with OR.
[Ozturk], 12/4/2020, retrospective, Turkey, Europe, peer-reviewed, 70 authors.	**risk of death, 43.9% lower, RR 0.56, *p* = 0.14**, treatment 165 of 1,127 (14.6%), control 6 of 23 (26.1%), NNT 8.7, CQ/HCQ.
[Paccoud], 6/18/2020, retrospective, France, Europe, peer-reviewed, 20 authors.	**risk of death, 11.0% lower, HR 0.89, *p* = 0.88**, treatment 21 of 38 (55.3%), control 26 of 46 (56.5%), NNT 79, adjusted per study.
[Pasquini], 8/23/2020, retrospective, Italy, Europe, peer-reviewed, 9 authors, excluded in exclusion analyses: unadjusted results	**risk of death, 16.4% lower, RR 0.84, *p* = 0.34**, treatment 23 of 33 (69.7%), control 15 of 18 (83.3%), NNT 7.3.

with no group details.	
[Peng], 12/4/2020, retrospective, China, Asia, peer-reviewed, 21 authors.	risk of progression, 10.8% lower, RR 0.89, $p = 0.63$, treatment 29 of 453 (6.4%), control 256 of 3,567 (7.2%), NNT 129, CQ/HCQ risk of AKI.
[Peters], 8/15/2020, retrospective, Netherlands, Europe, peer-reviewed, 21 authors, excluded in exclusion analyses: excessive unadjusted differences between groups.	risk of death, 9.0% higher, HR 1.09, $p = 0.57$, treatment 419 of 1,596 (26.3%), control 53 of 353 (15.0%), adjusted per study.
[Pinato], 8/18/2020, retrospective, multiple countries, multiple regions, peer-reviewed, 64 authors.	risk of death, 59.0% lower, HR 0.41, $p < 0.001$, treatment 30 of 182 (16.5%), control 181 of 446 (40.6%), NNT 4.1.
[Psevdos], 12/31/2020, retrospective, USA, North America, peer-reviewed, 3 authors, excluded in exclusion analyses: unadjusted results with no group details, no treatment details, substantial confounding by time likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically, substantial unadjusted confounding by indication likely.	risk of death, 63.5% higher, RR 1.63, $p = 0.52$, treatment 17 of 52 (32.7%), control 3 of 15 (20.0%).
[Purwati (B)], 2/9/2021, Double Blind Randomized Controlled Trial, Indonesia, South Asia, peer-reviewed, 12 authors.	risk of no viral clearance, 66.3% lower, RR 0.34, $p < 0.001$, treatment 38 of 121 (31.4%), control 111 of 119 (93.3%), NNT 1.6, day 7.
[Qin], 11/23/2020, retrospective, China, Asia, peer-reviewed, 17 authors, excluded in exclusion analyses: unadjusted results with no group details.	risk of death, 34.3% lower, RR 0.66, $p = 0.61$, treatment 3 of 43 (7.0%), control 75 of 706 (10.6%), NNT 27.
[Ramírez-García], 5/31/2021, retrospective, Spain, Europe, peer-reviewed, 5 authors, excluded in exclusion analyses: excessive unadjusted differences between groups, substantial unadjusted confounding by indication likely.	risk of death, 67.0% lower, RR 0.33, $p < 0.001$, treatment 48 of 350 (13.7%), control 22 of 53 (41.5%), NNT 3.6.
	risk of ICU admission, 6.0% higher, RR 1.06, $p = 1.00$, treatment 35 of 350 (10.0%), control 5 of 53 (9.4%).
[RECOVERY], 6/5/2020, Randomized Controlled Trial, United Kingdom, Europe, preprint, baseline oxygen required 76.8%, 29 authors, average treatment delay 9.0 days, trial NCT04381936, excluded in	risk of death, 9.0% higher, RR 1.09, $p = 0.15$, treatment 421 of 1,561 (27.0%), control 790 of 3,155 (25.0%).

exclusion analyses: excessive dosage in late stage patients, results do not apply to typical dosages.	
[Reis], 4/22/2021, Double Blind Randomized Controlled Trial, Brazil, South America, peer-reviewed, 18 authors, dosage 800mg day 1, 400mg days 2-10, trial NCT04403100 (TOGETHER).	**risk of death, 66.0% lower, RR 0.34, *p* = 1.00**, treatment 0 of 214 (0.0%), control 1 of 227 (0.4%), NNT 227, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of hospitalization, 24.0% lower, HR 0.76, *p* = 0.57, treatment 8 of 214 (3.7%), control 11 of 227 (4.8%), NNT 90, ITT, Cox proportional hazards.
	risk of no viral clearance, 4.1% lower, RR 0.96, *p* = 0.10, treatment 97 of 185 (52.4%), control 102 of 179 (57.0%), NNT 22, adjusted per study, odds ratio converted to relative risk, ITT, mixed-effect logistic model.
[Rivera], 7/22/2020, retrospective, USA, North America, peer-reviewed, 45 authors.	**risk of death, 2.4% higher, RR 1.02, *p* = 0.92**, treatment 44 of 179 (24.6%), control 59 of 327 (18.0%), adjusted per study, odds ratio converted to relative risk.
[Rivera-Izquierdo], 7/9/2020, retrospective, Spain, Europe, peer-reviewed, 21 authors.	**risk of death, 19.0% lower, RR 0.81, *p* = 0.75**, treatment 215, control 23.
[Rodriguez], 11/9/2020, prospective, Spain, Europe, peer-reviewed, 13 authors, average treatment delay 8.0 days, excluded in exclusion analyses: unadjusted results with no group details.	**risk of death, 59.0% lower, RR 0.41, *p* = 0.23**, treatment 8 of 39 (20.5%), control 2 of 4 (50.0%), NNT 3.4.
[Rodriguez-Gonzalez], 11/28/2020, retrospective, Spain, Europe, peer-reviewed, 20 authors, average treatment delay 6.0 days.	**risk of death, 22.8% lower, RR 0.77, *p* = 0.26**, treatment 251 of 1,148 (21.9%), control 17 of 60 (28.3%), NNT 15.
[Rodriguez-Nava], 11/5/2020, retrospective, USA, North America, peer-reviewed, median age 68.0, 8 authors, excluded in exclusion analyses: substantial unadjusted confounding by indication likely, excessive unadjusted differences between groups, unadjusted results with no group details.	**risk of death, 6.3% higher, RR 1.06, *p* = 0.77**, treatment 22 of 65 (33.8%), control 79 of 248 (31.9%), unadjusted.
[Rogado], 5/29/2020, retrospective, Spain, Europe, peer-reviewed, 9 authors.	**risk of death, 91.6% lower, RR 0.08, *p* = 0.02**, treatment 1 of 8 (12.5%), control 7 of 9 (77.8%), NNT

	1.5, odds ratio converted to relative risk, multivariate logistic regression.
[Roger], 7/10/2021, prospective, France, Europe, peer-reviewed, 34 authors, average treatment delay 8.0 days, excluded in exclusion analyses: substantial confounding by time likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically.	**risk of death, no change, RR 1.00, *p* = 0.94**, treatment 53 of 289 (18.3%), control 120 of 677 (17.7%), odds ratio converted to relative risk.
[Roig], 1/31/2021, retrospective, Spain, Europe, peer-reviewed, 6 authors, excluded in exclusion analyses: unadjusted results with no group details.	**risk of death, 15.6% lower, RR 0.84, *p* = 0.76**, treatment 33 of 67 (49.3%), control 7 of 12 (58.3%), NNT 11.
[Roomi], 8/13/2020, retrospective, USA, North America, peer-reviewed, 11 authors, excluded in exclusion analyses: substantial unadjusted confounding by indication likely.	**risk of death, 37.7% higher, RR 1.38, *p* = 0.54**, treatment 13 of 144 (9.0%), control 6 of 32 (18.8%), adjusted per study, odds ratio converted to relative risk.
[Rosenberg], 5/11/2020, retrospective, USA, North America, peer-reviewed, 14 authors.	**risk of death, 35.0% higher, HR 1.35, *p* = 0.31**, treatment 189 of 735 (25.7%), control 28 of 221 (12.7%), adjusted per study.
[Rosenthal], 12/10/2020, retrospective, database analysis, USA, North America, peer-reviewed, 5 authors, excluded in exclusion analyses: confounding by indication is likely and adjustments do not consider COVID-19 severity at baseline.	**risk of death, 8.0% higher, OR 1.08, *p* = 0.13**, adjusted per study, multivariable, RR approximated with OR.
[Rouamba], 2/26/2022, retrospective, Burkina Faso, Africa, peer-reviewed, mean age 42.2, 17 authors, study period 9 March, 2020 - 31 October, 2020, dosage 200mg tid days 1-10, HCQ 200mg tid daily or CQ 250mg bid daily, trial NCT04445441.	**risk of death, 80.0% lower, HR 0.20, *p* < 0.001**, treatment 20 of 336 (6.0%), control 24 of 73 (32.9%), NNT 3.7, adjusted per study, inpatients, multivariable, Cox proportional hazards.
	risk of progression, 20.0% lower, HR 0.80, *p* = 0.43, treatment 75 of 745 (10.1%), control 19 of 118 (16.1%), adjusted per study, all patients, multivariable, Cox proportional hazards.
	risk of progression, 7.0% higher, HR 1.07, *p* = 0.83, treatment 52 of 347 (15.0%), control 15 of 85 (17.6%), adjusted per study, inpatients, multivariable, Cox proportional hazards.

	time to viral clearance, 30.6% lower, HR 0.69, *p* = 0.26, treatment 746, control 118, adjusted per study, all patients, propensity score matching, multivariable, Cox proportional hazards, primary outcome.
	time to viral clearance, 13.0% lower, HR 0.87, *p* = 0.29, treatment 746, control 118, adjusted per study, all patients, without PSM, multivariable, Cox proportional hazards, primary outcome.
	time to viral clearance, 13.8% lower, HR 0.86, *p* = 0.37, treatment 345, control 86, adjusted per study, inpatients, multivariable, Cox proportional hazards, primary outcome.
[Réa-Neto], 4/27/2021, Randomized Controlled Trial, Brazil, South America, peer-reviewed, 6 authors, average treatment delay 8.0 days, trial NCT04420247.	risk of death, 57.0% higher, RR 1.57, *p* = 0.20, treatment 16 of 53 (30.2%), control 10 of 52 (19.2%).
	risk of mechanical ventilation, 115.0% higher, RR 2.15, *p* = 0.03, treatment 53, control 52.
	9-point scale clinical status, 147.0% higher, OR 2.47, *p* = 0.02, treatment 53, control 52, RR approximated with OR.
[Saib], 6/9/2021, prospective, propensity score matching, France, Europe, peer-reviewed, 9 authors, average treatment delay 7.2 days, excluded in exclusion analyses: substantial unadjusted confounding by indication likely.	risk of death/intubation, 125.0% higher, RR 2.25, *p* = 0.23, treatment 9 of 52 (17.3%), control 4 of 52 (7.7%), PSM.
[Salazar], 11/4/2020, retrospective, USA, North America, peer-reviewed, 19 authors, excluded in exclusion analyses: substantial unadjusted confounding by indication likely, unadjusted results with no group details.	risk of death, 37.0% higher, RR 1.37, *p* = 0.28, treatment 12 of 92 (13.0%), control 80 of 811 (9.9%).
[Saleemi], 8/11/2020, retrospective, Saudi Arabia, Middle East, preprint, 5 authors, excluded in exclusion analyses: substantial unadjusted confounding by indication likely.	median time to PCR-, 21.0% higher, relative time 1.21, *p* < 0.05, treatment 65, control 20.
[Salehi], 3/11/2022, retrospective, Iran, Middle East, preprint, mean age 62.0, 11 authors, study period April 2021 -	risk of death, 14.5% higher, RR 1.14, *p* = 0.44, treatment 53 of 86 (61.6%), control 21 of 39 (53.8%).

September 2021, excluded in exclusion analyses: unadjusted results with no group details.	
[Salvador], 3/4/2021, prospective, Portugal, Europe, peer-reviewed, 10 authors.	**risk of death, 32.9% lower, RR 0.67, p = 0.10**, treatment 28 of 121 (23.1%), control 58 of 124 (46.8%), NNT 4.2, odds ratio converted to relative risk, multivariate.
	risk of mechanical ventilation, 447.8% higher, RR 5.48, p = 0.003, treatment 32 of 121 (26.4%), control 12 of 124 (9.7%), odds ratio converted to relative risk, multivariate.
	risk of death/intubation, 16.7% lower, RR 0.83, p = 0.21, treatment 51 of 121 (42.1%), control 63 of 124 (50.8%), NNT 12, odds ratio converted to relative risk, univariate.
[Sammartino], 5/10/2021, retrospective, propensity score matching, USA, North America, peer-reviewed, 7 authors, excluded in exclusion analyses: substantial confounding by time likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically.	**risk of death, 240.0% higher, OR 3.40, p = 0.002**, treatment 137, control 191, PSM, model 1a, RR approximated with OR.
[Sands], 1/1/2021, retrospective, database analysis, USA, North America, peer-reviewed, 10 authors, excluded in exclusion analyses: includes PCR+ patients that may be asymptomatic for COVID-19 but in hospital for other reasons, substantial unadjusted confounding by indication likely.	**risk of death, 69.9% higher, RR 1.70, p = 0.01**, treatment 101 of 973 (10.4%), control 56 of 696 (8.0%), odds ratio converted to relative risk.
[Sarfaraz], 1/2/2021, retrospective, Pakistan, South Asia, preprint, 7 authors, average treatment delay 7.0 days, excluded in exclusion analyses: substantial unadjusted confounding by indication likely, significant unadjusted confounding possible, unadjusted results with no group details.	**risk of death, 45.0% higher, RR 1.45, p = 0.07**, treatment 40 of 94 (42.6%), control 27 of 92 (29.3%).
[Sarhan], 11/2/2021, Randomized Controlled Trial, Egypt, Africa, peer-reviewed, 8 authors, study period 1	**risk of death, 25.7% lower, RR 0.74, p = 0.39**, treatment 12 of 56 (21.4%), control 15 of 52 (28.8%), NNT 13.

October, 2020 - 10 March, 2021, this trial compares with another treatment - results may be better when compared to placebo, trial NCT04779047, excluded in exclusion analyses: very late stage, >50% on oxygen/ventilation at baseline, significant unadjusted differences between groups.	risk of no hospital discharge, 25.7% lower, RR 0.74, *p* = 0.39, treatment 12 of 56 (21.4%), control 15 of 52 (28.8%), NNT 13.
	hospitalization time, 25.0% higher, relative time 1.25, *p* = 0.06, treatment 56, control 52.
[Sbidian], 6/19/2020, retrospective, database analysis, France, Europe, preprint, 21 authors, excluded in exclusion analyses: significant issues found with adjustments.	**risk of death, 5.0% higher, RR 1.05, *p* = 0.74**, treatment 111 of 623 (17.8%), control 830 of 3,792 (21.9%), adjusted per study, whole population HCQ AIPTW adjusted.
	risk of no hospital discharge, 20.0% lower, RR 0.80, *p* = 0.002, treatment 623, control 3,792, adjusted per study, whole population HCQ AIPTW adjusted.
[Schmidt], 11/12/2021, retrospective, USA, North America, peer-reviewed, 42 authors, study period 17 March, 2020 - 11 February, 2021, excluded in exclusion analyses: confounding by indication is likely and adjustments do not consider COVID-19 severity at baseline.	**risk of death, 333.0% higher, OR 4.33, *p* < 0.001**, treatment 70, control 407, adjusted per study, propensity score matching, multivariable, RR approximated with OR.
	risk of severe case, 613.0% higher, OR 7.13, *p* < 0.001, treatment 70, control 407, adjusted per study, propensity score matching, multivariable, RR approximated with OR.
[Schwartz], 6/18/2021, Double Blind Randomized Controlled Trial, Canada, North America, peer-reviewed, 20 authors, average treatment delay 7.0 days, dosage 800mg day 1, 400mg days 2-5.	**risk of ICU admission, 133.3% higher, RR 2.33, *p* = 1.00**, treatment 1 of 111 (0.9%), control 0 of 37 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm).
	risk of hospitalization, 533.3% higher, RR 6.33, *p* = 0.57, treatment 4 of 111 (3.6%), control 0 of 37 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm).
	risk of ICU admission, 141.9% higher, RR 2.42, *p* = 1.00, treatment 1 of 74 (1.4%), control 0 of 31 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm), per-protocol.
	risk of hospitalization, 141.9% higher, RR 2.42, *p* = 1.00, treatment 1 of 74 (1.4%), control 0 of 31 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm), per-protocol.
[Self], 11/9/2020, Randomized Controlled Trial, USA, North America, peer-reviewed,	**risk of death, 6.2% higher, RR 1.06, *p* = 0.85**, treatment 25 of 241 (10.4%), control 25 of 236

33 authors, average treatment delay 5.0 days.	(10.6%), NNT 455, adjusted per study, odds ratio converted to relative risk.
[Serrano], 9/22/2020, retrospective, Spain, Europe, peer-reviewed, 8 authors.	**risk of death, 43.0% lower, RR 0.57, p = 0.14**, treatment 6 of 14 (42.9%), control 6 of 8 (75.0%), NNT 3.1.
[Shabrawishi], 5/11/2020, retrospective, Saudi Arabia, Middle East, preprint, mean age 43.9, 5 authors.	**risk of no virological cure at day 5, 14.7% lower, RR 0.85, p = 0.66**, treatment 12 of 45 (26.7%), control 15 of 48 (31.2%), NNT 22.
[Sheshah], 11/13/2020, retrospective, Saudi Arabia, Middle East, peer-reviewed, 8 authors.	**risk of death, 80.0% lower, RR 0.20, p < 0.001**, treatment 267, control 33, odds ratio converted to relative risk.
[Shoaibi], 9/24/2020, retrospective, database analysis, USA, North America, preprint, 5 authors, excluded in exclusion analyses: unadjusted results with no group details.	**risk of death, 15.4% lower, RR 0.85, p < 0.001**, treatment 686 of 5,047 (13.6%), control 3,923 of 24,404 (16.1%), NNT 40.
[Signes-Costa], 12/16/2020, retrospective, multiple countries, multiple regions, peer-reviewed, 28 authors.	**risk of death, 47.0% lower, RR 0.53, p < 0.001**, treatment 4,854, control 993, adjusted per study.
[Silva], 5/20/2022, retrospective, Brazil, South America, peer-reviewed, mean age 58.4, 28 authors, study period 25 March, 2020 - 21 October, 2020.	**risk of death, 46.1% higher, RR 1.46, p = 0.21**, treatment 21, control 374, adjusted per study, odds ratio converted to relative risk, multivariable, control prevalance approximated with overall prevalence.
[Singh (B)], 6/8/2021, Randomized Controlled Trial, India, South Asia, preprint, 13 authors, this trial uses multiple treatments in the treatment arm (combined with ribavirin) - results of individual treatments may vary.	**risk of death, 47.5% lower, RR 0.53, p = 0.45**, treatment 3 of 20 (15.0%), control 6 of 21 (28.6%), NNT 7.4, severe.
	risk of death, 50.0% lower, RR 0.50, p = 0.48, treatment 3 of 37 (8.1%), control 6 of 37 (16.2%), NNT 12, all patients.
	risk of no recovery, 14.1% lower, RR 0.86, p = 0.76, treatment 9 of 20 (45.0%), control 11 of 21 (52.4%), NNT 14, severe.
	risk of no recovery, 8.3% lower, RR 0.92, p = 1.00, treatment 11 of 37 (29.7%), control 12 of 37 (32.4%), NNT 37, all patients.
[Singh], 5/19/2020, retrospective, database analysis, USA, North America, preprint, 4 authors, excluded in exclusion analyses:	**risk of death, 5.0% lower, RR 0.95, p = 0.72**, treatment 104 of 910 (11.4%), control 109 of 910 (12.0%), NNT 182.

confounding by indication is likely and adjustments do not consider COVID-19 severity at baseline.	risk of mechanical ventilation, 19.0% lower, RR 0.81, *p* = 0.26, treatment 46 of 910 (5.1%), control 57 of 910 (6.3%), NNT 83.
[Sivapalan], 6/3/2021, Double Blind Randomized Controlled Trial, Denmark, Europe, peer-reviewed, 32 authors, average treatment delay 8.0 days, trial NCT04322396.	**risk of death, 92.0% lower, RR 0.08, *p* = 0.32**, treatment 1 of 61 (1.6%), control 2 of 56 (3.6%), adjusted per study.
	risk of ICU admission, 22.4% higher, RR 1.22, *p* = 1.00, treatment 4 of 61 (6.6%), control 3 of 56 (5.4%).
	relative days alive and discharged from hospital within 14 days (inverse), 8.4% worse, RR 1.08, *p* = 0.36, treatment 61, control 56, adjusted per study.
[Smith], 5/31/2021, retrospective, USA, North America, preprint, 4 authors, excluded in exclusion analyses: immortal time bias may significantly affect results.	**risk of death, 27.2% lower, RR 0.73, *p* = 0.002**, treatment 19 of 37 (51.4%), control 182 of 218 (83.5%), NNT 3.1, odds ratio converted to relative risk, >3g HCQ and >1g AZ, multivariable cox proportional hazard regression.
[Solh], 10/20/2020, retrospective, database analysis, USA, North America, preprint, 5 authors, excluded in exclusion analyses: very late stage, >50% on oxygen/ventilation at baseline, substantial unadjusted confounding by indication likely.	**risk of death, 18.0% higher, HR 1.18, *p* = 0.17**, treatment 131 of 265 (49.4%), control 134 of 378 (35.4%), adjusted per study.
[SOLIDARITY], 10/15/2020, Randomized Controlled Trial, multiple countries, multiple regions, peer-reviewed, baseline oxygen required 64.0%, 15 authors, excluded in exclusion analyses: excessive dosage in late stage patients, results do not apply to typical dosages, very late stage, >50% on oxygen/ventilation at baseline.	**risk of death, 19.0% higher, RR 1.19, *p* = 0.23**, treatment 104 of 947 (11.0%), control 84 of 906 (9.3%).
[Sosa-García], 6/29/2020, retrospective, Mexico, North America, peer-reviewed, baseline oxygen required 100.0%, 6 authors, average treatment delay 9.0 days, excluded in exclusion analyses: very late stage, >50% on oxygen/ventilation at baseline, substantial unadjusted confounding by indication likely.	**risk of death, 10.5% higher, RR 1.11, *p* = 1.00**, treatment 7 of 38 (18.4%), control 3 of 18 (16.7%).
[Soto], 3/2/2022, retrospective, Peru, South America, peer-reviewed, median age 58.0, 10 authors, study period April 2020 -	**risk of death, 6.0% higher, HR 1.06, *p* = 0.46**, treatment 292 of 590 (49.5%), control 362 of 828 (43.7%), Cox proportional hazards.

August 2020, dosage not specified, excluded in exclusion analyses: unadjusted results with no group details, substantial unadjusted confounding by indication likely, substantial confounding by time possible due to significant changes in SOC and treatment propensity near the start of the pandemic.	
[Soto-Becerra], 10/8/2020, retrospective, database analysis, Peru, South America, preprint, median age 59.4, 4 authors, study period 1 April, 2020 - 19 July, 2020, excluded in exclusion analyses: substantial unadjusted confounding by indication likely, includes PCR+ patients that may be asymptomatic for COVID-19 but in hospital for other reasons.	**risk of death, 18.1% lower, HR 0.82, $p < 0.001$**, treatment 346 of 692 (50.0%), control 1,606 of 2,630 (61.1%), NNT 9.0, day 54 (last day available) weighted KM.
	risk of death, 84.0% higher, HR 1.84, $p = 0.02$, treatment 165 of 692 (23.8%), control 401 of 2,630 (15.2%), adjusted per study, day 30.
[Stewart], 3/17/2021, retrospective, USA, North America, peer-reviewed, 37 authors, excluded in exclusion analyses: substantial unadjusted confounding by indication likely, substantial confounding by time likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically, includes PCR+ patients that may be asymptomatic for COVID-19 but in hospital for other reasons.	**risk of death, 18.0% higher, RR 1.18, $p = 0.27$**, treatment 90 of 429 (21.0%), control 141 of 737 (19.1%), adjusted per study, VA, HCQ+AZ.
[Stewart (B)], 3/17/2021, retrospective, USA, North America, peer-reviewed, 37 authors, excluded in exclusion analyses: substantial unadjusted confounding by indication likely, substantial confounding by time likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically, includes PCR+ patients that may be asymptomatic for COVID-19 but in hospital for other reasons.	**risk of mechanical ventilation, 29.0% higher, RR 1.29, $p = 0.09$**, treatment 48 of 305 (15.7%), control 95 of 1,302 (7.3%), adjusted per study, Aetion, HCQ.
[Stewart (C)], 3/17/2021, retrospective, USA, North America, peer-reviewed, 37 authors, excluded in exclusion analyses: substantial unadjusted confounding by indication likely, substantial confounding by time likely due to declining usage over the early stages of the pandemic when overall	**risk of death, 16.0% higher, RR 1.16, $p = 0.26$**, treatment 428 of 1,711 (25.0%), control 123 of 688 (17.9%), adjusted per study, COTA/HMH, HCQ+AZ.

treatment protocols improved dramatically, includes PCR+ patients that may be asymptomatic for COVID-19 but in hospital for other reasons.	
[Stewart (D)], 3/17/2021, retrospective, USA, North America, peer-reviewed, 37 authors, excluded in exclusion analyses: substantial unadjusted confounding by indication likely, substantial confounding by time likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically, includes PCR+ patients that may be asymptomatic for COVID-19 but in hospital for other reasons.	risk of death, 90.0% higher, RR 1.90, $p = 0.09$, treatment 46 of 208 (22.1%), control 47 of 1,334 (3.5%), adjusted per study, Dascena, HCQ+AZ.
[Stewart (E)], 3/17/2021, retrospective, USA, North America, peer-reviewed, 37 authors, excluded in exclusion analyses: substantial unadjusted confounding by indication likely, substantial confounding by time likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically, includes PCR+ patients that may be asymptomatic for COVID-19 but in hospital for other reasons.	risk of death, 9.0% higher, RR 1.09, $p = 0.65$, treatment 212 of 1,157 (18.3%), control 203 of 1,101 (18.4%), NNT 873, adjusted per study, Health Catalyst, HCQ+AZ.
[Stewart (F)], 3/17/2021, retrospective, USA, North America, peer-reviewed, 37 authors, excluded in exclusion analyses: substantial unadjusted confounding by indication likely, substantial confounding by time likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically, includes PCR+ patients that may be asymptomatic for COVID-19 but in hospital for other reasons.	risk of death, 129.9% higher, RR 2.30, $p < 0.001$, treatment 32 of 108 (29.6%), control 33 of 256 (12.9%), Synapse, HCQ+AZ.
[Stewart (G)], 3/17/2021, retrospective, USA, North America, peer-reviewed, 37 authors, excluded in exclusion analyses: substantial unadjusted confounding by indication likely, substantial confounding by time likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically,	risk of death, 1.0% lower, RR 0.99, $p = 0.95$, treatment 66 of 578 (11.4%), control 188 of 1,243 (15.1%), adjusted per study, TriNetX, HCQ+AZ.

includes PCR+ patients that may be asymptomatic for COVID-19 but in hospital for other reasons.	
[Synolaki], 9/5/2020, retrospective, Greece, Europe, preprint, 20 authors.	risk of death, 23.6% lower, RR 0.76, $p = 0.27$, treatment 21 of 98 (21.4%), control 60 of 214 (28.0%), NNT 15.
[Sánchez-Álvarez], 4/27/2020, retrospective, database analysis, Spain, Europe, peer-reviewed, mean age 67.0, 10 authors.	risk of death, 45.9% lower, RR 0.54, $p = 0.005$, treatment 322, control 53, odds ratio converted to relative risk.
[Taccone], 12/23/2020, retrospective, Belgium, Europe, peer-reviewed, 10 authors, average treatment delay 5.0 days.	risk of death, 24.7% lower, RR 0.75, $p = 0.02$, treatment 449 of 1,308 (34.3%), control 183 of 439 (41.7%), NNT 14, odds ratio converted to relative risk.
[Taieb], 6/30/2021, retrospective, Senegal, Africa, peer-reviewed, 29 authors, average treatment delay 6.0 days.	risk of no hospital discharge, 38.7% lower, OR 0.61, $p = 0.02$, treatment 674, control 252, multivariate, RR approximated with OR.
[Tamura], 7/13/2021, retrospective, Brazil, South America, peer-reviewed, 4 authors, study period 10 March, 2020 - 13 November, 2020, excluded in exclusion analyses: substantial unadjusted confounding by indication likely, substantial confounding by time likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically.	risk of death, 299.0% higher, OR 3.99, $p = 0.04$, treatment 25, control 163, adjusted per study, multivariable, RR approximated with OR.
[Tan], 12/14/2020, retrospective, China, Asia, peer-reviewed, 7 authors.	hospitalization time, 35.2% lower, relative time 0.65, $p = 0.04$, treatment 8, control 277.
[Tang], 4/14/2020, Randomized Controlled Trial, China, Asia, peer-reviewed, 24 authors, average treatment delay 16.6 days.	risk of no virological cure at day 21, 21.4% lower, RR 0.79, $p = 0.51$, treatment 11 of 75 (14.7%), control 14 of 75 (18.7%), NNT 25.
[Tehrani], 10/30/2020, retrospective, Sweden, Europe, peer-reviewed, 5 authors, excluded in exclusion analyses: substantial unadjusted confounding by indication likely, unadjusted results with no group details.	risk of death, 13.4% lower, RR 0.87, $p = 0.63$, treatment 16 of 65 (24.6%), control 54 of 190 (28.4%), NNT 26.
[Texeira], 12/31/2020, retrospective, USA, North America, peer-reviewed, 6 authors, excluded in exclusion analyses: unadjusted	risk of death, 79.3% higher, RR 1.79, $p = 0.10$, treatment 17 of 65 (26.2%), control 14 of 96 (14.6%).

results with no group details, no treatment details, substantial confounding by time likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically, substantial unadjusted confounding by indication likely.	
[Thompson], 2/9/2021, Double Blind Randomized Controlled Trial, USA, North America, preprint, 1 author.	**risk of death, 6.2% higher, RR 1.06, p = 0.85**, treatment 25 of 241 (10.4%), control 25 of 236 (10.6%), NNT 455, adjusted per study, odds ratio converted to relative risk, day 28.
	risk of death, 51.0% higher, RR 1.51, p = 0.28, treatment 18 of 241 (7.5%), control 14 of 236 (5.9%), adjusted per study, odds ratio converted to relative risk, day 14.
	risk of 7-point scale, 3.1% higher, OR 1.03, p = 0.87, treatment 241, control 236, day 28, RR approximated with OR.
	risk of 7-point scale, 2.0% lower, OR 0.98, p = 0.91, treatment 241, control 236, day 14, RR approximated with OR.
[Trullàs], 7/14/2020, retrospective, Spain, Europe, preprint, median age 75.0, 8 authors, average treatment delay 9.0 days.	**risk of death, 35.6% lower, RR 0.64, p = 0.12**, treatment 20 of 66 (30.3%), control 16 of 34 (47.1%), NNT 6.0.
[Tsanovska], 3/3/2022, prospective, Bulgaria, Europe, peer-reviewed, 8 authors, study period 6 November, 2020 - 28 December, 2020.	**risk of death, 57.9% lower, RR 0.42, p = 0.03**, treatment 8 of 70 (11.4%), control 19 of 70 (27.1%), NNT 6.4, propensity score matching.
	risk of mechanical ventilation, 73.9% lower, RR 0.26, p < 0.001, treatment 6 of 70 (8.6%), control 23 of 70 (32.9%), NNT 4.1, propensity score matching.
	risk of ICU admission, 70.4% lower, RR 0.30, p < 0.001, treatment 8 of 70 (11.4%), control 27 of 70 (38.6%), NNT 3.7, propensity score matching.
[Tu], 1/13/2022, retrospective, Sierraleone, Africa, peer-reviewed, 11 authors, study period 31 March, 2020 - 11 August, 2020, excluded in exclusion analyses: unadjusted results with no group details.	**risk of death, 17.2% lower, RR 0.83, p = 0.81**, treatment 6 of 37 (16.2%), control 28 of 143 (19.6%), NNT 30.
[Turrini], 6/11/2021, retrospective, Italy,	**risk of death, 9.8% lower, RR 0.90, p = 0.15**,

Europe, peer-reviewed, 16 authors.	treatment 103 of 160 (64.4%), control 33 of 45 (73.3%), NNT 11, adjusted per study, odds ratio converted to relative risk, multivariate.
[Ubaldo], 2/1/2021, retrospective, Philippines, Asia, peer-reviewed, 3 authors, excluded in exclusion analyses: substantial unadjusted confounding by indication likely, very late stage, ICU patients, unadjusted results with no group details.	**risk of death, 18.4% lower, RR 0.82, *p* = 0.64**, treatment 17 of 25 (68.0%), control 5 of 6 (83.3%), NNT 6.5, COVID-19 positive patients.
[Ulrich], 9/23/2020, Randomized Controlled Trial, USA, North America, peer-reviewed, baseline oxygen required 63.3%, mean age 66.2, 18 authors, average treatment delay 7.0 days, excluded in exclusion analyses: very late stage, >50% on oxygen/ventilation at baseline.	**risk of death, 6.0% higher, RR 1.06, *p* = 1.00**, treatment 7 of 67 (10.4%), control 6 of 61 (9.8%).
[Uyaroğlu], 3/17/2022, retrospective, propensity score matching, Turkey, Europe, peer-reviewed, 6 authors, study period 20 March, 2020 - 30 September, 2020, this trial compares with another treatment - results may be better when compared to placebo.	**risk of death, 200.0% higher, RR 3.00, *p* = 1.00**, treatment 1 of 42 (2.4%), control 0 of 42 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm).
	risk of ICU admission, 66.7% lower, RR 0.33, *p* = 1.00, treatment 0 of 42 (0.0%), control 1 of 42 (2.4%), NNT 42, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	hospitalization time, 9.8% lower, relative time 0.90, *p* = 0.90, treatment 42, control 42.
[Uygen], 9/15/2021, retrospective, Turkey, Europe, peer-reviewed, 4 authors.	**time to viral-, 12.2% lower, relative time 0.88, *p* = 0.05**, treatment 15, control 25.
[van Halem], 11/27/2020, retrospective, Belgium, Europe, peer-reviewed, 10 authors.	**risk of death, 31.6% lower, RR 0.68, *p* = 0.05**, treatment 34 of 164 (20.7%), control 47 of 155 (30.3%), NNT 10.
[Vernaz], 12/31/2020, retrospective, propensity score matching, Switzerland, Europe, peer-reviewed, 15 authors, excluded in exclusion analyses: substantial confounding by time likely due to declining usage over the early stages of the pandemic when overall treatment	**risk of death, 15.3% lower, RR 0.85, *p* = 0.71**, treatment 12 of 93 (12.9%), control 16 of 105 (15.2%), NNT 43, HCQ vs. SOC, PSM.
	hospitalization time, 49.0% higher, relative time 1.49, *p* = 0.002, treatment 93, control 105, HCQ vs. SOC, PSM.

protocols improved dramatically, substantial unadjusted confounding by indication likely.	
[Wang (C)], 6/10/2020, retrospective, database analysis, USA, North America, preprint, 3 authors, excluded in exclusion analyses: confounding by indication is likely and adjustments do not consider COVID-19 severity at baseline.	**risk of death, 5.8% lower, RR 0.94, *p* = 0.63**, treatment 1,866, control 5,726, odds ratio converted to relative risk.
[Xia], 2/11/2020, retrospective, China, Asia, preprint, 1 author, excluded in exclusion analyses: minimal details provided.	**risk of no viral clearance, 37.5% lower, RR 0.62, *p* = 0.17**, treatment 5 of 10 (50.0%), control 12 of 15 (80.0%), NNT 3.3.
[Yegerov], 1/8/2021, retrospective, Kazakhstan, Asia, preprint, 8 authors, average treatment delay 1.0 days, excluded in exclusion analyses: unadjusted results with no group details.	**risk of death, 95.3% lower, RR 0.05, *p* = 1.00**, treatment 0 of 23 (0.0%), control 20 of 1,049 (1.9%), NNT 52, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
[Yu (B)], 8/3/2020, retrospective, China, Asia, preprint, median age 62.0, 6 authors.	**risk of progression to critical, 82.5% lower, RR 0.17, *p* = 0.049**, treatment 1 of 231 (0.4%), control 32 of 1,291 (2.5%), NNT 49, baseline critical cohort reported separately in Yu et al..
	risk of death, 85.0% lower, RR 0.15, *p* = 0.02, treatment 1 of 73 (1.4%), control 238 of 2,604 (9.1%), NNT 13, HCQ treatment started early vs. non-HCQ.
[Yu (C)], 5/15/2020, retrospective, China, Asia, peer-reviewed, 8 authors.	**risk of death, 60.5% lower, RR 0.40, *p* = 0.002**, treatment 9 of 48 (18.8%), control 238 of 502 (47.4%), NNT 3.5.
[Zhong], 3/26/2020, retrospective, China, Asia, preprint, 1 author.	**risk of no virological cure at day 10, 80.0% lower, RR 0.20, *p* < 0.001**, treatment 5 of 115 (4.3%), control 17 of 82 (20.7%), NNT 6.1, adjusted per study.
[Águila-Gordo], 11/11/2020, retrospective, Spain, Europe, peer-reviewed, mean age 84.4, 6 authors.	**risk of death, 67.0% lower, RR 0.33, *p* = 0.10**, treatment 151 of 346 (43.6%), control 47 of 70 (67.1%), NNT 4.3, adjusted per study.
[Çivriz Bozdağ], 9/15/2021, retrospective, Turkey, Europe, peer-reviewed, 62 authors, excluded in exclusion analyses: substantial confounding by time likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically.	**risk of death, 399.2% higher, RR 4.99, *p* = 0.003**, treatment 35, control 140.

[Çiyiltepe], 4/30/2021, retrospective, Turkey, Europe, peer-reviewed, 5 authors, excluded in exclusion analyses: treatment group only includes patients where treatment failed resulting in ICU admission.	**risk of death, 3.2% lower, RR 0.97, *p* = 0.85**, treatment 69 of 95 (72.6%), control 39 of 52 (75.0%), NNT 42.
[Ñamendys-Silva], 10/21/2020, retrospective, database analysis, Mexico, North America, peer-reviewed, mean age 57.3, 18 authors, average treatment delay 7.0 days.	**risk of death, 32.3% lower, RR 0.68, *p* = 0.18**, treatment 24 of 54 (44.4%), control 42 of 64 (65.6%), NNT 4.7, HCQ+AZ vs. neither HCQ or CQ.
	risk of death, 37.1% lower, RR 0.63, *p* = 0.09, treatment 19 of 46 (41.3%), control 42 of 64 (65.6%), NNT 4.1, CQ vs. neither HCQ or CQ.
	risk of death, 34.5% lower, RR 0.66, *p* = 0.006, treatment 43 of 100 (43.0%), control 42 of 64 (65.6%), NNT 4.4, HCQ+AZ or CQ.

Pre-Exposure Prophylaxis

Effect extraction follows pre-specified rules as detailed above and gives priority to more serious outcomes. Only the first (most serious) outcome is used in pooled analysis, which may differ from the effect a paper focuses on. Other outcomes are used in outcome specific analyses.

[Abella], 9/30/2020, Randomized Controlled Trial, USA, North America, peer-reviewed, 18 authors.	**risk of case, 5.0% lower, RR 0.95, *p* = 1.00**, treatment 4 of 64 (6.2%), control 4 of 61 (6.6%), NNT 325.
[Agarwal], 9/14/2021, prospective, India, South Asia, preprint, 1 author.	**risk of hospitalization, 94.8% lower, RR 0.05, *p* = 0.61**, treatment 0 of 29 (0.0%), control 17 of 455 (3.7%), NNT 27, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	relative severity, 26.9% better, RR 0.73, *p* = 0.21, treatment 29, control 455.
	risk of case, 4.6% higher, RR 1.05, *p* = 0.81, treatment 6 of 29 (20.7%), control 90 of 455 (19.8%).
[Ahmed], 11/23/2021, retrospective, Saudi Arabia, Middle East, peer-reviewed, 7 authors.	**risk of case, 99.3% lower, OR 0.007, *p* = 0.08**, treatment 0 of 50 (0.0%) cases, 13 of 50 (26.0%) controls, NNT 1.7, case control OR.
[Alegiani], 4/15/2021, retrospective, case control, database analysis, Italy, Europe, peer-reviewed, 16 authors.	**risk of death, 8.0% higher, OR 1.08, *p* = 0.64**, HCQ vs. other cDMARDs, RR approximated with OR.
	risk of hospitalization, 18.0% lower, OR 0.82, *p* = 0.03,

	HCQ vs. other cDMARDs, RR approximated with OR.
	risk of death, 19.0% higher, OR 1.19, *p* = 0.32, HCQ vs. MTX, RR approximated with OR.
	risk of hospitalization, 12.0% lower, OR 0.88, *p* = 0.17, HCQ vs. MTX, RR approximated with OR.
[Alzahrani], 4/15/2021, retrospective, Saudi Arabia, Middle East, peer-reviewed, 3 authors.	**risk of death, 58.7% lower, RR 0.41, *p* = 1.00**, treatment 0 of 14 (0.0%), control 1 of 33 (3.0%), NNT 33, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of mechanical ventilation, 81.0% lower, RR 0.19, *p* = 0.54, treatment 0 of 14 (0.0%), control 3 of 33 (9.1%), NNT 11, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of severe case, 32.7% lower, RR 0.67, *p* = 0.70, treatment 2 of 14 (14.3%), control 7 of 33 (21.2%), NNT 14.
[Arleo], 10/27/2020, retrospective, USA, North America, preprint, 5 authors.	**risk of death, 50.0% lower, RR 0.50, *p* = 0.67**, treatment 1 of 20 (5.0%), control 5 of 50 (10.0%), NNT 20, all patients.
	risk of death, 52.0% lower, RR 0.48, *p* = 0.64, treatment 1 of 10 (10.0%), control 5 of 24 (20.8%), NNT 9.2, inpatients.
[Badyal], 6/7/2021, prospective, India, South Asia, peer-reviewed, 18 authors.	**risk of case, 60.1% lower, RR 0.40, *p* < 0.001**, treatment 247 of 617 (40.0%), control 611 of 1,473 (41.5%), adjusted per study, odds ratio converted to relative risk, >=6 weeks, logistic regression.
	risk of case, 35.1% lower, RR 0.65, *p* = 0.003, treatment 88 of 185 (47.6%), control 611 of 1,473 (41.5%), adjusted per study, odds ratio converted to relative risk, 4-5 weeks, logistic regression.
	risk of case, 23.2% lower, RR 0.77, *p* = 0.04, treatment 80 of 181 (44.2%), control 611 of 1,473 (41.5%), adjusted per study, odds ratio converted to relative risk, 2-3 weeks, logistic regression.
[Bae], 2/20/2021, retrospective, propensity score matching, South Korea, Asia, peer-	**risk of case, 30.3% lower, RR 0.70, *p* = 0.18**, treatment 16 of 743 (2.2%), control 91 of 2,698

reviewed, 8 authors.	(3.4%), NNT 82, odds ratio converted to relative risk, PSM.
	risk of case, 19.5% lower, RR 0.81, *p* = 0.50, treatment 16 of 743 (2.2%), control 91 of 2,698 (3.4%), odds ratio converted to relative risk, PSM, adjusted for region.
	risk of case, 30.3% lower, RR 0.70, *p* = 0.30, treatment 16 of 743 (2.2%), control 91 of 2,698 (3.4%), NNT 82, odds ratio converted to relative risk, PSM, adjusted for immunosuppresant use.
	risk of case, 40.2% lower, RR 0.60, *p* = 0.09, odds ratio converted to relative risk, PSM, HCQ >= 6 months.
[Behera], 11/3/2020, retrospective, India, South Asia, peer-reviewed, 13 authors.	**risk of case, 27.9% lower, RR 0.72, *p* = 0.29**, treatment 7 of 19 (36.8%), control 179 of 353 (50.7%), NNT 7.2, adjusted per study, odds ratio converted to relative risk, model 2 conditional logistic regression.
	risk of case, 26.3% lower, RR 0.74, *p* = 0.25, treatment 7 of 19 (36.8%), control 179 of 353 (50.7%), NNT 7.2, odds ratio converted to relative risk, matched pair analysis.
[Belmont], 10/6/2021, prospective, USA, North America, preprint, 1 author, trial NCT04354870.	**risk of symptomatic case, 78.6% lower, RR 0.21, *p* = 0.21**, treatment 1 of 56 (1.8%), control 2 of 24 (8.3%), NNT 15.
	risk of case, 14.3% lower, RR 0.86, *p* = 1.00, treatment 4 of 56 (7.1%), control 2 of 24 (8.3%), NNT 84.
[Bhatt], 8/4/2021, prospective, India, South Asia, preprint, 4 authors.	**risk of case, 49.3% higher, RR 1.49, *p* = 0.02**, treatment 167 of 731 (22.8%), control 30 of 196 (15.3%).
[Bhattacharya], 6/9/2020, retrospective, India, South Asia, preprint, 7 authors.	**risk of case, 80.7% lower, RR 0.19, *p* = 0.001**, treatment 4 of 54 (7.4%), control 20 of 52 (38.5%), NNT 3.2.
[Cassione], 5/12/2020, retrospective, Italy, Europe, preprint, survey, median age 52.5, 6 authors, excluded in exclusion analyses: not fully adjusting for the different baseline risk of systemic autoimmune patients.	**risk of case, 49.6% higher, RR 1.50, *p* = 0.59**, treatment 10 of 127 (7.9%), control 2 of 38 (5.3%).
[Chatterjee], 5/28/2020, retrospective, India, South Asia, peer-reviewed, survey, 11	**risk of case, 66.8% lower, RR 0.33, *p* < 0.001**, treatment 12 of 68 (17.6%), control 206 of 387

authors.	(53.2%), NNT 2.8, full course vs. unused.
[Cordtz], 8/27/2021, retrospective, population-based cohort, Denmark, Europe, peer-reviewed, 8 authors, study period 1 March, 2020 - 2 February, 2021.	**risk of hospitalization, 40.0% lower, HR 0.60, *p* = 0.39**, treatment 1,170, control 1,363, adjusted per study.
[Cordtz (B)], 12/28/2020, retrospective, population-based cohort, Denmark, Europe, peer-reviewed, 10 authors.	**risk of hospitalization, 24.0% lower, HR 0.76, *p* = 0.67**, treatment 3 of 2,722 (0.1%), control 38 of 26,718 (0.1%), NNT 3124, adjusted per study, time-dependent exposure model.
	risk of hospitalization, 55.0% lower, HR 0.45, *p* = 0.28, treatment 3 of 2,722 (0.1%), control 38 of 26,718 (0.1%), adjusted per study, time-fixed exposure model.
[Datta], 11/6/2020, retrospective, India, South Asia, peer-reviewed, 7 authors.	**risk of case, 22.1% lower, RR 0.78, *p* = 0.47**, treatment 16 of 146 (11.0%), control 19 of 135 (14.1%), NNT 32.
[de la Iglesia], 9/2/2020, retrospective, database analysis, Spain, Europe, preprint, 17 authors, excluded in exclusion analyses: not fully adjusting for the different baseline risk of systemic autoimmune patients.	**risk of hospitalization, 50.0% higher, RR 1.50, *p* = 1.00**, treatment 3 of 687 (0.4%), control 2 of 688 (0.3%).
	risk of case, 42.6% higher, RR 1.43, *p* = 0.15, treatment 42 of 648 (6.5%), control 30 of 660 (4.5%), suspected COVID-19.
	risk of case, 7.8% lower, RR 0.92, *p* = 0.84, treatment 12 of 678 (1.8%), control 13 of 677 (1.9%), NNT 665, confirmed COVID-19.
[Del Amo], 3/4/2022, Double Blind Randomized Controlled Trial, placebo-controlled, multiple countries, multiple regions, preprint, 1 author, study period April 2020 - May 2021, dosage 200mg daily, trial NCT04334928.	**risk of symptomatic case, 51.0% lower, RR 0.49, *p* = 0.79**, treatment 3 of 231 (1.3%), control 5 of 223 (2.2%), NNT 106, HCQ, Kaplan–Meier.
	risk of symptomatic case, 61.0% lower, RR 0.39, *p* = 0.72, treatment 3 of 220 (1.4%), control 5 of 223 (2.2%), TDF+HCQ, Kaplan–Meier.
	risk of case, 27.0% lower, RR 0.73, *p* = 0.31, treatment 21 of 231 (9.1%), control 23 of 223 (10.3%), HCQ, Kaplan–Meier.
	risk of case, 49.0% lower, RR 0.51, *p* = 0.09, treatment 13 of 220 (5.9%), control 23 of 223 (10.3%), NNT 23, TDF+HCQ, Kaplan–Meier.

[Desbois], 7/20/2020, retrospective, France, Europe, preprint, mean age 58.8, 13 authors.	**risk of case, 16.9% lower, RR 0.83, p = 1.00**, treatment 3 of 27 (11.1%), control 23 of 172 (13.4%), NNT 44.
[Dev], 3/24/2021, retrospective, India, South Asia, peer-reviewed, 5 authors.	**risk of case, 26.0% lower, RR 0.74, p = 0.003**, treatment 260, control 499, any number of HCQ doses vs. no HCQ prophylaxis.
[Erden], 1/23/2022, retrospective, Turkey, Europe, peer-reviewed, 11 authors, excluded in exclusion analyses: unadjusted results with no group details.	**risk of death, 150.0% higher, RR 2.50, p = 1.00**, treatment 1 of 6 (16.7%), control 0 of 3 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm).
	risk of hospitalization, 75.0% lower, RR 0.25, p = 0.23, treatment 1 of 6 (16.7%), control 2 of 3 (66.7%), NNT 2.0.
[Ferreira (B)], 6/29/2020, retrospective, population-based cohort, database analysis, Portugal, Europe, peer-reviewed, 3 authors.	**risk of case, 47.1% lower, RR 0.53, p < 0.001**, adjusted per study, odds ratio converted to relative risk.
[Ferri], 8/27/2020, retrospective, Italy, Europe, peer-reviewed, survey, 29 authors.	**risk of COVID-19 case, 63.0% lower, RR 0.37, p = 0.01**, treatment 9 of 994 (0.9%), control 16 of 647 (2.5%), NNT 64.
[Fitzgerald], 2/5/2021, retrospective, USA, North America, preprint, 34 authors, excluded in exclusion analyses: not fully adjusting for the baseline risk differences within systemic autoimmune patients.	**risk of case, 8.5% lower, RR 0.91, p = 0.54**, treatment 65 of 1,072 (6.1%), control 200 of 3,594 (5.6%), adjusted per study, odds ratio converted to relative risk.
[Fung], 10/1/2021, retrospective, population-based cohort, USA, North America, peer-reviewed, 6 authors, excluded in exclusion analyses: not fully adjusting for the different baseline risk of systemic autoimmune patients.	**risk of death, 13.0% lower, HR 0.87, p = 0.15**, vs. past use (better match for systemic autoimmune diseases).
	risk of hospitalization, 3.0% lower, HR 0.97, p = 0.63, vs. past use (better match for systemic autoimmune diseases).
	risk of case, 9.0% lower, HR 0.91, p = 0.02, vs. past use (better match for systemic autoimmune diseases).
	risk of death, 8.0% higher, HR 1.08, p = 0.26, vs. never used.
	risk of hospitalization, 6.0% higher, HR 1.06, p = 0.13, vs. never used.

	risk of case, 5.0% lower, HR 0.95, p = 0.03, vs. never used.
[Gendebien], 6/25/2020, retrospective, Belgium, Europe, preprint, survey, 9 authors, excluded in exclusion analyses: not fully adjusting for the baseline risk differences within systemic autoimmune patients.	**risk of case, 3.9% lower, RR 0.96, p = 0.93**, treatment 12 of 152 (7.9%), control 6 of 73 (8.2%), NNT 308.
[Gendelman], 5/5/2020, retrospective, database analysis, Israel, Middle East, peer-reviewed, 5 authors, excluded in exclusion analyses: not fully adjusting for the different baseline risk of systemic autoimmune patients.	**risk of case, 8.1% lower, RR 0.92, p = 0.88**, treatment 3 of 36 (8.3%), control 1,314 of 14,484 (9.1%), NNT 135.
[Gentry], 9/21/2020, retrospective, database analysis, USA, North America, peer-reviewed, 6 authors.	**risk of death, 91.3% lower, RR 0.09, p = 0.10**, treatment 0 of 10,703 (0.0%), control 7 of 21,406 (0.0%), NNT 3058, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), COVID-19 mortality within all patients.
	risk of death, 90.7% lower, RR 0.09, p = 0.19, treatment 0 of 31 (0.0%), control 7 of 78 (9.0%), NNT 11, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), mortality for infected patients.
	risk of case, 20.9% lower, RR 0.79, p = 0.27, treatment 31 of 10,703 (0.3%), control 78 of 21,406 (0.4%), NNT 1338, odds ratio converted to relative risk.
[Gianfrancesco], 5/28/2020, retrospective, database analysis, multiple countries, multiple regions, peer-reviewed, 28 authors, excluded in exclusion analyses: not fully adjusting for the baseline risk differences within systemic autoimmune patients.	**risk of hospitalization, 3.3% lower, RR 0.97, p = 0.82**, treatment 58 of 130 (44.6%), control 219 of 470 (46.6%), NNT 50, odds ratio converted to relative risk.
[Goenka], 10/24/2020, retrospective, India, South Asia, preprint, 11 authors.	**risk of IgG positive, 87.2% lower, RR 0.13, p = 0.03**, treatment 1 of 77 (1.3%), control 115 of 885 (13.0%), NNT 8.6, adjusted per study, odds ratio converted to relative risk.
[Grau-Pujol], 9/21/2020, Randomized Controlled Trial, Spain, Europe, peer-reviewed, 22 authors.	**risk of case, 10.6% lower, RR 0.89, p = 1.00**, treatment 1 of 142 (0.7%), control 1 of 127 (0.8%), NNT 1202.

[Gönenli], 12/16/2020, retrospective, Turkey, Europe, preprint, survey, 4 authors.	**risk of pneumonia, 29.7% lower, RR 0.70, p = 0.77**, treatment 3 of 148 (2.0%), control 12 of 416 (2.9%), NNT 117.
	risk of case, 18.9% higher, RR 1.19, p = 0.58, treatment 8 of 148 (5.4%), control 20 of 416 (4.8%), odds ratio converted to relative risk.
[Huang], 6/16/2020, retrospective, China, Asia, peer-reviewed, 15 authors, excluded in exclusion analyses: significant unadjusted confounding possible.	**risk of hospitalization, 80.0% lower, RR 0.20, p < 0.001**, treatment 8, control 1,247.
[Huh], 12/19/2020, retrospective, database analysis, South Korea, Asia, peer-reviewed, 8 authors, excluded in exclusion analyses: not fully adjusting for the different baseline risk of systemic autoimmune patients.	**risk of progression, 251.0% higher, RR 3.51, p = 0.11**, treatment 5 of 8 (62.5%), control 873 of 2,797 (31.2%), adjusted per study, multivariate.
	risk of case, 6.0% lower, RR 0.94, p = 0.82, treatment 17 of 122 (13.9%), control 7,324 of 43,924 (16.7%), adjusted per study, multivariate.
[Juneja], 1/7/2022, retrospective, India, South Asia, peer-reviewed, 9 authors, study period 2 April, 2020 - 3 September, 2020, excluded in exclusion analyses: excessive unadjusted differences between groups.	**risk of severe case, 141.8% higher, RR 2.42, p = 0.59**, treatment 2 of 996 (0.2%), control 1 of 1,204 (0.1%).
	risk of case, 6.4% higher, RR 1.06, p = 0.67, treatment 103 of 996 (10.3%), control 117 of 1,204 (9.7%).
[Jung], 12/11/2020, retrospective, South Korea, Asia, peer-reviewed, 6 authors.	**risk of death, 59.3% lower, RR 0.41, p = 1.00**, treatment 0 of 649 (0.0%), control 1 of 1,417 (0.1%), NNT 1417, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of case, 13.1% higher, RR 1.13, p = 0.86, treatment 15 of 649 (2.3%), control 31 of 1,417 (2.2%), adjusted per study.
[Kadnur], 7/22/2020, prospective, India, South Asia, peer-reviewed, mean age 31.2, 16 authors, study period 23 April, 2020 - 11 June, 2020.	**risk of case, 62.3% lower, RR 0.38, p = 0.01**, treatment 10 of 258 (3.9%), control 15 of 100 (15.0%), NNT 9.0, odds ratio converted to relative risk, multivariate logistic regression.
[Kamstrup], 6/1/2021, retrospective, population-based cohort, Denmark, Europe, peer-reviewed, 21 authors, excluded in exclusion analyses: not fully adjusting for the different baseline risk of systemic autoimmune patients.	**risk of hospitalization, 44.0% higher, OR 1.44, p = 0.25**, treatment 5,488, control 54,846, RR approximated with OR.
	risk of case, 10.0% lower, HR 0.90, p = 0.23, treatment 188 of 5,488 (3.4%), control 2,040 of 54,846 (3.7%), NNT 340, adjusted Cox proportional hazards

	regression.
[Khoubnasabjafari], 1/13/2021, retrospective, Iran, Middle East, peer-reviewed, 10 authors.	**risk of case, 16.7% lower, RR 0.83, *p* = 0.59**, treatment 34 of 1,436 (2.4%), control 12 of 422 (2.8%), NNT 210.
[Khurana], 7/24/2020, retrospective, India, South Asia, preprint, survey, 5 authors.	**risk of case, 51.0% lower, RR 0.49, *p* = 0.02**, treatment 6 of 22 (27.3%), control 88 of 159 (55.3%), NNT 3.6, odds ratio converted to relative risk.
[Konig], 5/7/2020, retrospective, database analysis, multiple countries, multiple regions, preprint, 11 authors, excluded in exclusion analyses: not fully adjusting for the baseline risk differences within systemic autoimmune patients.	**risk of hospitalization, 3.0% lower, RR 0.97, *p* = 0.88**, treatment 16 of 29 (55.2%), control 29 of 51 (56.9%), NNT 59.
[Korkmaz], 6/1/2021, retrospective, Turkey, Europe, preprint, 4 authors.	**risk of death, 82.1% lower, RR 0.18, *p* = 0.19**, treatment 0 of 385 (0.0%), control 2 of 299 (0.7%), NNT 150, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of case, 93.7% lower, RR 0.06, $p < 0.001$, treatment 2 of 395 (0.5%), control 24 of 299 (8.0%), NNT 13.
[Küçükakkaş], 7/20/2021, retrospective, Turkey, Europe, preprint, 2 authors, excluded in exclusion analyses: minimal details of groups provided.	**risk of ICU admission, 42.9% higher, RR 1.43, *p* = 1.00**, treatment 1 of 7 (14.3%), control 1 of 10 (10.0%).
[Laplana], 9/9/2020, retrospective, Spain, Europe, peer-reviewed, survey, 3 authors, excluded in exclusion analyses: not fully adjusting for the different baseline risk of systemic autoimmune patients.	**risk of case, 56.0% higher, RR 1.56, *p* = 0.24**, treatment 17 of 319 (5.3%), control 11 of 319 (3.4%).
[MacFadden], 3/29/2022, retrospective, Canada, North America, peer-reviewed, 9 authors, study period 15 January, 2020 - 31 December, 2020.	**risk of case, 12.0% lower, OR 0.88, *p* = 0.01**, RR approximated with OR.
[Macias], 5/16/2020, retrospective, database analysis, Spain, Europe, preprint, 12 authors, excluded in exclusion analyses: not fully adjusting for the baseline risk differences within systemic autoimmune patients.	**risk of hospitalization, 25.5% lower, RR 0.74, *p* = 1.00**, treatment 1 of 290 (0.3%), control 2 of 432 (0.5%), NNT 846.
	risk of case, 49.0% higher, RR 1.49, *p* = 0.53, treatment 5 of 290 (1.7%), control 5 of 432 (1.2%).

[Mahto], 2/15/2021, retrospective, India, South Asia, peer-reviewed, 6 authors, excluded in exclusion analyses: unadjusted results with no group details.	**risk of IgG positive, 26.9% lower, RR 0.73, $p = 0.38$**, treatment 9 of 89 (10.1%), control 84 of 600 (14.0%), NNT 26, unadjusted, odds ratio converted to relative risk.
[Mathai], 11/6/2020, retrospective, India, South Asia, peer-reviewed, 3 authors.	**risk of case, 89.5% lower, RR 0.10, $p < 0.001$**, treatment 10 of 491 (2.0%), control 22 of 113 (19.5%), NNT 5.7.
	risk of case, 88.5% lower, RR 0.12, $p < 0.001$, treatment 5 of 491 (1.0%), control 10 of 113 (8.8%), NNT 13, symptomatic.
[McKinnon], 12/23/2021, Double Blind Randomized Controlled Trial, USA, North America, peer-reviewed, 10 authors, trial NCT04341441.	**risk of symptomatic case, 2.5% lower, RR 0.98, $p = 1.00$**, treatment 2 of 365 (0.5%), control 1 of 178 (0.6%), NNT 7219, daily and weekly HCQ combined.
	risk of symptomatic case, no change, RR 1.00, $p = 1.00$, treatment 1 of 178 (0.6%), control 1 of 178 (0.6%), daily HCQ.
	risk of symptomatic case, 4.8% lower, RR 0.95, $p = 1.00$, treatment 1 of 187 (0.5%), control 1 of 178 (0.6%), NNT 3698, weekly HCQ.
	risk of symptomatic case, 53.3% lower, RR 0.47, $p = 1.00$, treatment 0 of 25 (0.0%), control 1 of 178 (0.6%), NNT 178, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), AD patients.
	risk of case, 51.2% lower, RR 0.49, $p = 0.60$, treatment 2 of 365 (0.5%), control 2 of 178 (1.1%), NNT 174, daily and weekly HCQ combined.
	risk of case, 50.0% lower, RR 0.50, $p = 1.00$, treatment 1 of 178 (0.6%), control 2 of 178 (1.1%), NNT 178, daily HCQ.
	risk of case, 52.4% lower, RR 0.48, $p = 0.61$, treatment 1 of 187 (0.5%), control 2 of 178 (1.1%), NNT 170, weekly HCQ.
	risk of case, 69.5% lower, RR 0.30, $p = 1.00$, treatment 0 of 25 (0.0%), control 2 of 178 (1.1%), NNT 89, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), AD patients.

[Mitchell], 5/5/2020, retrospective, multiple countries, multiple regions, preprint, 2 authors, excluded in exclusion analyses: excessive unadjusted differences between groups.	**risk of death, 99.0% lower, RR 0.01, $p < 0.001$**.
[Naggie], 8/25/2021, Randomized Controlled Trial, USA, North America, preprint, 22 authors, trial NCT04334148.	**risk of symptomatic case, 23.5% lower, RR 0.76, $p = 0.18$**, treatment 41 of 683 (6.0%), control 53 of 676 (7.8%), NNT 54, odds ratio converted to relative risk, logistic regression.
	risk of symptomatic case, 29.3% lower, RR 0.71, $p = 0.18$, treatment 41 of 683 (6.0%), control 53 of 676 (7.8%), NNT 54, odds ratio converted to relative risk, Mantel–Haenszel.
[Opdam], 2/23/2022, retrospective, Netherlands, Europe, peer-reviewed, 9 authors.	**risk of hospitalization, 45.0% lower, OR 0.55, $p = 0.18$**, treatment 8 of 81 (9.9%) cases, 59 of 396 (14.9%) controls, NNT 17, case control OR.
[Oztas], 3/21/2022, retrospective, Turkey, Europe, peer-reviewed, 15 authors, excluded in exclusion analyses: not adjusting for the different baseline risk of systemic autoimmune patients, excessive unadjusted differences between groups.	**risk of hospitalization, 215.1% higher, RR 3.15, $p = 0.36$**, treatment 3 of 317 (0.9%), control 1 of 333 (0.3%).
	risk of symptomatic case, 40.1% higher, RR 1.40, $p = 0.44$, treatment 16 of 317 (5.0%), control 12 of 333 (3.6%).
	risk of case, 5.0% higher, RR 1.05, $p = 0.88$, treatment 22 of 317 (6.9%), control 22 of 333 (6.6%).
[Patil], 8/24/2021, prospective, India, South Asia, preprint, 20 authors.	**risk of death, 65.9% lower, RR 0.34, $p = 0.10$**, treatment 5,266, control 3,946.
	risk of case, 9.1% lower, RR 0.91, $p = 0.43$, treatment 167 of 5,266 (3.2%), control 147 of 3,946 (3.7%), NNT 181, adjusted per study.
[Pham], 3/2/2021, retrospective, USA, North America, peer-reviewed, 5 authors.	**risk of death, 19.7% lower, RR 0.80, $p = 0.77$**, treatment 2 of 14 (14.3%), control 5 of 28 (17.9%), NNT 28, odds ratio converted to relative risk, univariate.
	risk of ICU admission, 35.5% higher, RR 1.35, $p = 0.61$, treatment 4 of 14 (28.6%), control 6 of 28 (21.4%), odds ratio converted to relative risk, univariate.
[Rajasingham], 9/21/2020, Randomized Controlled Trial, USA, North America, peer-	**risk of hospitalization, 50.1% lower, RR 0.50, $p = 1.00$**, treatment 1 of 989 (0.1%), control 1 of 494

reviewed, 22 authors, trial NCT04328467.	(0.2%), NNT 987.
	risk of case, 27.0% lower, HR 0.73, *p* = 0.12, treatment 58 of 989 (5.9%), control 39 of 494 (7.9%), NNT 49.
[Rangel], 1/10/2021, retrospective, USA, North America, peer-reviewed, 5 authors, excluded in exclusion analyses: not fully adjusting for the different baseline risk of systemic autoimmune patients.	**risk of death, 25.1% lower, RR 0.75, *p* = 0.77**, treatment 4 of 50 (8.0%), control 11 of 103 (10.7%), NNT 37, from all patients.
	risk of hospitalization, 22.2% lower, RR 0.78, *p* = 0.29, treatment 17 of 50 (34.0%), control 45 of 103 (43.7%), NNT 10.
	hospitalization time, 41.2% lower, relative time 0.59, *p* = 0.12, treatment 21, control 54.
[Rao], 12/4/2021, prospective, India, South Asia, peer-reviewed, 8 authors, excluded in exclusion analyses: unadjusted results with minimal group details.	**risk of case, 11.0% lower, RR 0.89, *p* = 0.68**, treatment 16 of 273 (5.9%), control 67 of 1,021 (6.6%), NNT 143.
[Rentsch], 9/9/2020, retrospective, population-based cohort, database analysis, United Kingdom, Europe, peer-reviewed, 34 authors, excluded in exclusion analyses: not fully adjusting for the baseline risk differences within systemic autoimmune patients, medication adherence unknown and may significantly change results.	**risk of death, 3.0% higher, HR 1.03, *p* = 0.83**, treatment 70 of 30,569 (0.2%), control 477 of 164,068 (0.3%), adjusted per study.
[Revollo], 11/21/2020, retrospective, propensity score matching, Spain, Europe, peer-reviewed, 16 authors.	**risk of case, 23.0% lower, RR 0.77, *p* = 0.52**, treatment 16 of 69 (23.2%), control 65 of 418 (15.6%), adjusted per study, PSM, risk of PCR+.
	risk of case, 43.0% higher, RR 1.43, *p* = 0.42, treatment 17 of 60 (28.3%), control 62 of 404 (15.3%), adjusted per study, PSM, risk of IgG+.
[Rojas-Serrano], 5/16/2021, Double Blind Randomized Controlled Trial, Mexico, North America, preprint, 8 authors, trial NCT04318015.	**risk of symptomatic case, 82.0% lower, RR 0.18, *p* = 0.12**, treatment 1 of 62 (1.6%), control 6 of 65 (9.2%), NNT 13, adjusted per study.
[Salvarani], 8/6/2020, retrospective, population-based cohort, Italy, Europe, peer-reviewed, 18 authors, excluded in	**risk of case, 6.0% lower, OR 0.94, *p* = 0.75**, RR approximated with OR.

exclusion analyses: not fully adjusting for the different baseline risk of systemic autoimmune patients.	
[Samajdar], 11/17/2021, retrospective, India, South Asia, peer-reviewed, 9 authors, study period 1 September, 2020 - 31 December, 2020, dosage not specified, excluded in exclusion analyses: minimal details provided, unadjusted results with no group details, results may be significantly affected by survey bias.	**risk of case, 74.5% lower, RR 0.25, $p < 0.001$**, treatment 12 of 129 (9.3%), control 29 of 81 (35.8%), NNT 3.8, odds ratio converted to relative risk, physician survey.
	risk of case, 48.6% lower, RR 0.51, $p = 0.03$, treatment 11 of 109 (10.1%), control 39 of 200 (19.5%), NNT 11, odds ratio converted to relative risk, combined ivermectin or HCQ in community.
[Satti], 4/22/2022, retrospective, Qatar, Middle East, peer-reviewed, 6 authors, excluded in exclusion analyses: unadjusted results with no group details.	**risk of case, 61.5% lower, RR 0.39, $p = 0.04$**, treatment 10 of 63 (15.9%), control 7 of 17 (41.2%), NNT 4.0.
[Shaw], 7/1/2021, retrospective, USA, North America, peer-reviewed, 10 authors, study period 1 March, 2020 - 15 May, 2020.	**risk of case, 13.0% lower, OR 0.87, $p = 0.006$**, treatment 45, control 99, adjusted per study, propensity score matching, multivariable, RR approximated with OR.
[Singer], 8/5/2020, retrospective, database analysis, USA, North America, preprint, 3 authors, excluded in exclusion analyses: not fully adjusting for the baseline risk differences within systemic autoimmune patients.	**risk of case, 9.0% higher, RR 1.09, $p = 0.62$**, treatment 55 of 10,700 (0.5%), control 104 of 22,058 (0.5%).
[Syed], 5/17/2021, Randomized Controlled Trial, Pakistan, South Asia, peer-reviewed, 8 authors, trial NCT04359537.	**risk of symptomatic case, 59.7% higher, RR 1.60, $p = 0.41$**, treatment 10 of 48 (20.8%), control 6 of 46 (13.0%), group 1.
	risk of symptomatic case, 110.5% higher, RR 2.10, $p = 0.13$, treatment 14 of 51 (27.5%), control 6 of 46 (13.0%), group 2.
	risk of symptomatic case, 16.4% lower, RR 0.84, $p = 0.77$, treatment 6 of 55 (10.9%), control 6 of 46 (13.0%), NNT 47, group 3.
	risk of case, 91.7% higher, RR 1.92, $p = 0.12$, treatment 15 of 38 (39.5%), control 7 of 34 (20.6%), group 1.
	risk of case, 136.6% higher, RR 2.37, $p = 0.02$, treatment 19 of 39 (48.7%), control 7 of 34 (20.6%),

	group 2.
	risk of case, 21.4% higher, RR 1.21, *p* = 0.77, treatment 8 of 32 (25.0%), control 7 of 34 (20.6%), group 3.
[Trefond], 1/27/2021, retrospective, France, Europe, peer-reviewed, 21 authors, excluded in exclusion analyses: not fully adjusting for the different baseline risk of systemic autoimmune patients, significant unadjusted confounding possible, excessive unadjusted differences between groups.	**risk of death, 16.6% higher, RR 1.17, *p* = 0.80**, treatment 4 of 68 (5.9%), control 12 of 183 (6.6%), adjusted per study, odds ratio converted to relative risk.
	risk of death/ICU, 78.2% higher, RR 1.78, *p* = 0.21, treatment 8 of 71 (11.3%), control 18 of 191 (9.4%), adjusted per study, odds ratio converted to relative risk.
	risk of hospitalization, 44.9% higher, RR 1.45, *p* = 0.12, treatment 24 of 71 (33.8%), control 53 of 191 (27.7%), adjusted per study, odds ratio converted to relative risk.
[Ugarte-Gil], 2/16/2022, retrospective, multiple countries, multiple regions, peer-reviewed, 58 authors.	**risk of severe case, 44.4% lower, OR 0.56, *p* = 0.007**, treatment 665, control 230, adjusted per study, HCQ/CQ only vs. no SLE medication, multivariable, RR approximated with OR.
[Vivanco-Hidalgo], 3/9/2021, retrospective, Spain, Europe, peer-reviewed, 8 authors, excluded in exclusion analyses: not fully adjusting for the different baseline risk of systemic autoimmune patients.	**risk of hospitalization, 46.0% higher, RR 1.46, *p* = 0.10**, treatment 40 of 6,746 (0.6%), control 50 of 13,492 (0.4%), adjusted per study.
	risk of case, 8.0% higher, RR 1.08, *p* = 0.50, treatment 97 of 6,746 (1.4%), control 183 of 13,492 (1.4%), adjusted per study.
[Yadav (B)], 9/30/2020, retrospective, India, South Asia, preprint, 11 authors.	**risk of hospitalization, 82.4% lower, RR 0.18, *p* = 0.01**, treatment 2 of 279 (0.7%), control 9 of 221 (4.1%), NNT 30, PCR+.
	risk of IgG+, 41.8% lower, RR 0.58, *p* = 0.049, treatment 17 of 178 (9.6%), control 27 of 221 (12.2%), odds ratio converted to relative risk, multivariate logistic regression.
	risk of IgG+, 79.0% lower, RR 0.21, *p* = 0.09, treatment 1 of 39 (2.6%), control 27 of 221 (12.2%), NNT 10, HCQ >10 weeks.
	risk of IgG+, 52.4% lower, RR 0.48, *p* = 0.14, treatment 5 of 86 (5.8%), control 27 of 221 (12.2%), NNT 16,

	HCQ 6-10 weeks.
	risk of IgG+, 69.9% higher, RR 1.70, *p* = 0.12, treatment 11 of 53 (20.8%), control 27 of 221 (12.2%), HCQ <6 weeks.
[Zhong (B)], 7/3/2020, retrospective, database analysis, China, Asia, peer-reviewed, 20 authors.	**risk of case, 91.0% lower, RR 0.09, *p* = 0.04**, treatment 7 of 16 (43.8%), control 20 of 27 (74.1%), NNT 3.3, adjusted per study.

Post-Exposure Prophylaxis

Effect extraction follows pre-specified rules as detailed above and gives priority to more serious outcomes. Only the first (most serious) outcome is used in pooled analysis, which may differ from the effect a paper focuses on. Other outcomes are used in outcome specific analyses.

[Barnabas], 12/7/2020, Randomized Controlled Trial, USA, North America, peer-reviewed, 30 authors, trial NCT04328961.	**risk of hospitalization, 3.7% higher, RR 1.04, *p* = 1.00**, treatment 1 of 407 (0.2%), control 1 of 422 (0.2%).
	risk of case, 27.0% higher, HR 1.27, *p* = 0.33, treatment 43 of 353 (12.2%), control 33 of 336 (9.8%), adjusted per study, day 14 symptomatic mITT PCR+ AIM.
	risk of case, 23.0% higher, HR 1.23, *p* = 0.41, treatment 40 of 317 (12.6%), control 32 of 309 (10.4%), adjusted per study, day 14 symptomatic mITT PCR+ IDWeek.
	risk of case, 10.0% higher, HR 1.10, *p* = 0.66, treatment 53 of 353 (15.0%), control 45 of 336 (13.4%), adjusted per study, day 14 PCR+ mITT AIM.
	risk of case, 1.0% lower, HR 0.99, *p* = 0.97, treatment 46 of 317 (14.5%), control 43 of 309 (13.9%), adjusted per study, day 14 PCR+ mITT IDWeek.
	risk of case, 19.0% lower, HR 0.81, *p* = 0.23, treatment 82 of 387 (21.2%), control 99 of 393 (25.2%), NNT 25, adjusted per study, day 14 PCR+ ITT AIM.
[Boulware (B)], 6/3/2020, Randomized Controlled Trial, USA, North America, peer-reviewed, 24 authors, this trial compares with another treatment - results may be better when compared to placebo.	**risk of case, 17.0% lower, RR 0.83, *p* = 0.35**, treatment 49 of 414 (11.8%), control 58 of 407 (14.3%), NNT 41.
	risk of case, 25.1% lower, RR 0.75, *p* = 0.22, treatment 32 of 414 (7.7%), control 42 of 407 (10.3%), NNT 39, probable COVID-19 cases.

[Dhibar], 11/6/2020, prospective, India, South Asia, peer-reviewed, 13 authors, trial NCT04408456.	**risk of case, 41.0% lower, RR 0.59, p = 0.03**, treatment 14 of 132 (10.6%), control 36 of 185 (19.5%), NNT 11, adjusted per study.
	risk of case, 50.0% lower, RR 0.50, p = 0.04, treatment 10 of 132 (7.6%), control 28 of 185 (15.1%), NNT 13, adjusted per study, PCR+.
	risk of symptomatic case, 43.9% lower, RR 0.56, p = 0.21, treatment 6 of 132 (4.5%), control 15 of 185 (8.1%), NNT 28, adjusted per study.
[Mitjà (B)], 7/26/2020, Randomized Controlled Trial, Spain, Europe, peer-reviewed, 12 authors.	**risk of death, 45.6% lower, RR 0.54, p = 0.39**, treatment 4 of 1,196 (0.3%), control 8 of 1,301 (0.6%), NNT 357, per supplemental appendix table S7, excluding patient that did not take any study medication and had an unknown cause of death.
	risk of hospitalization, 16.8% lower, RR 0.83, p = 0.71, treatment 13 of 1,196 (1.1%), control 17 of 1,301 (1.3%), NNT 455, per supplemental appendix table S7, excluding patient that did not take any study medication and had an unknown cause of death.
	baseline PCR- risk of cases, 32.0% lower, RR 0.68, p = 0.27, treatment 29 of 958 (3.0%), control 45 of 1,042 (4.3%), NNT 77.
[Polat], 9/30/2020, prospective, Turkey, Europe, peer-reviewed, 3 authors.	**risk of case, 57.0% lower, RR 0.43, p = 0.03**, treatment 12 of 138 (8.7%), control 14 of 70 (20.0%), NNT 8.8.
[Seet], 4/14/2021, Cluster Randomized Controlled Trial, Singapore, Asia, peer-reviewed, 15 authors, dosage 400mg day 1, 200mg days 2-42, this trial compares with another treatment - results may be better when compared to placebo, trial NCT04446104.	**risk of symptomatic case, 35.1% lower, RR 0.65, p = 0.047**, treatment 29 of 432 (6.7%), control 64 of 619 (10.3%), NNT 28.
	risk of case, 32.0% lower, RR 0.68, p = 0.009, treatment 212 of 432 (49.1%), control 433 of 619 (70.0%), NNT 4.8, adjusted per study, odds ratio converted to relative risk, model 6.
[Shabani], 8/10/2021, prospective, Iran, Middle East, peer-reviewed, 16 authors.	**risk of symptomatic case, 19.0% lower, RR 0.81, p = 1.00**, treatment 2 of 51 (3.9%), control 3 of 62 (4.8%), NNT 109, day 7.
	risk of case, 6.4% higher, RR 1.06, p = 1.00, treatment 7 of 51 (13.7%), control 8 of 62 (12.9%), day 7, PCR+ and symptomatic.

	risk of case, 21.6% higher, RR 1.22, p = 0.78, treatment 7 of 51 (13.7%), control 7 of 62 (11.3%), day 7, PCR+ only.
[Simova (B)], 11/12/2020, retrospective, Bulgaria, Europe, peer-reviewed, 5 authors.	risk of case, 92.7% lower, RR 0.07, p = 0.01, treatment 0 of 156 (0.0%), control 3 of 48 (6.2%), NNT 16, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).

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